VOLUME 53 NUMBER 1 JANUARY 1960

PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

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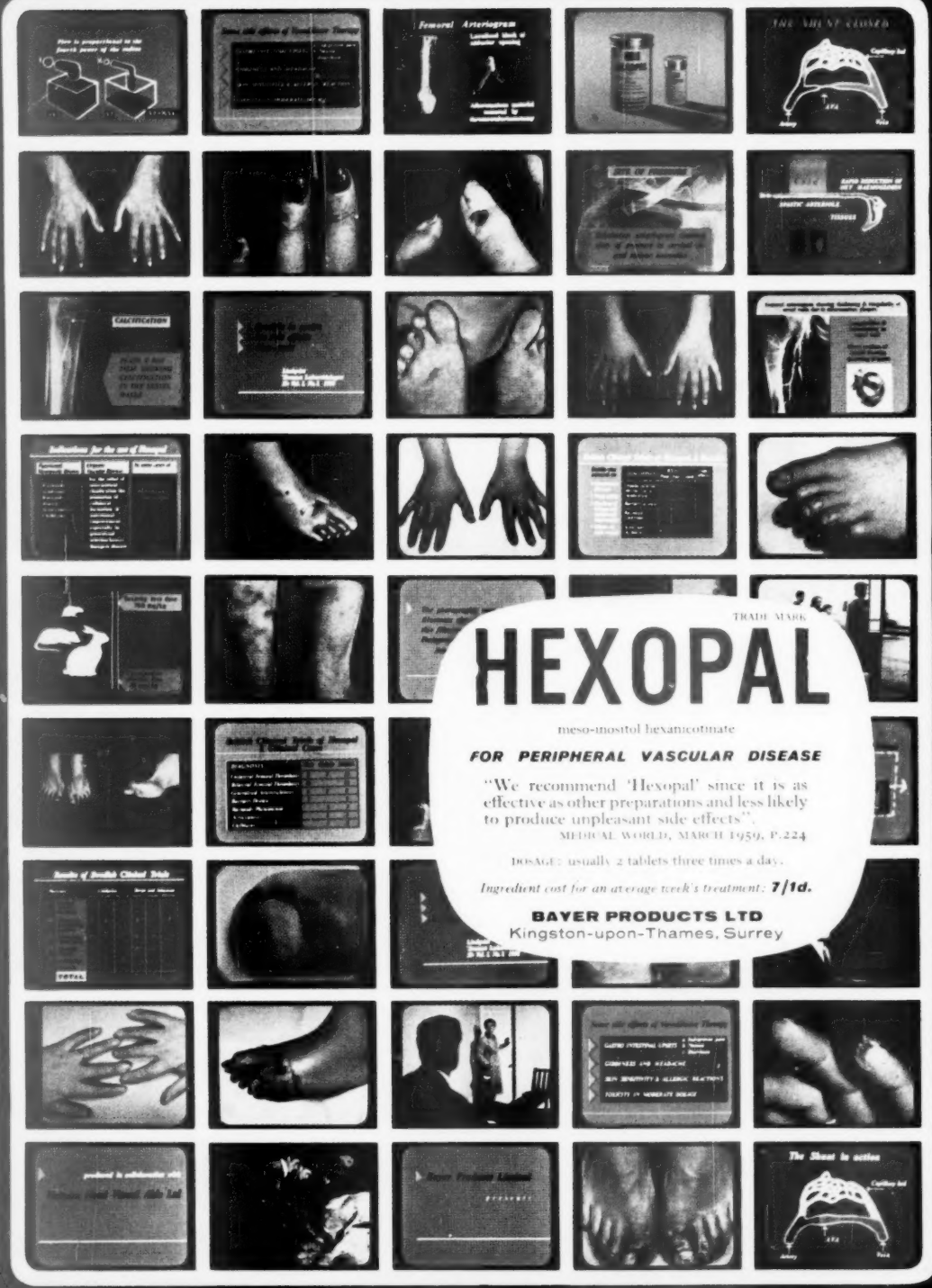

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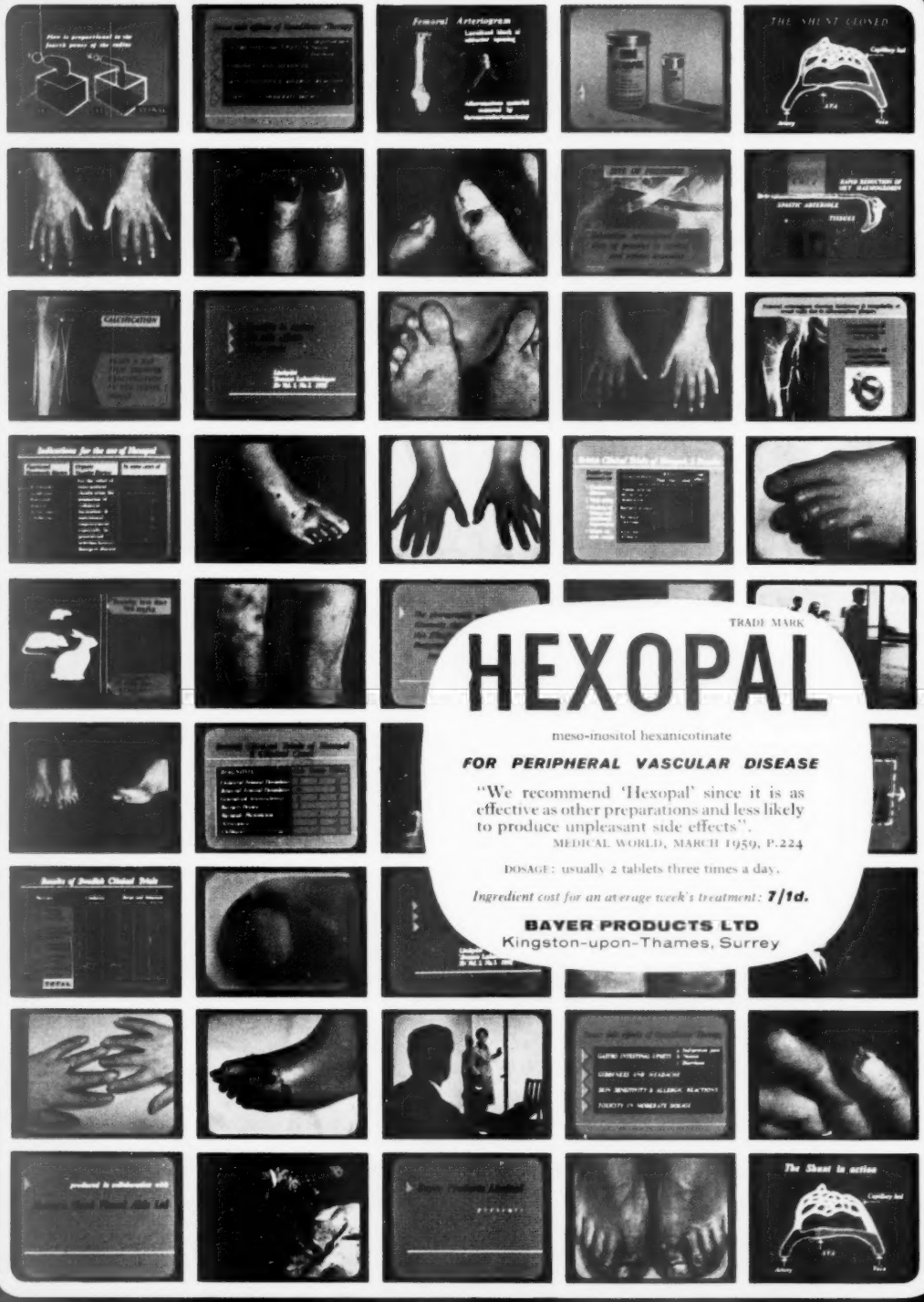

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of the

ROYAL SOCIETY OF MEDICINE

Vol. 53 No. 1 January 1960

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N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

"In general practice at least

40% of patients have symptoms

of functional disorder..."

Lancet (1958) **1**, 525

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"BARBITURATE DEATHS INCREASING"

Under this warning headline British Medical Journal, in an editorial of October 17th, 1959, draws attention to the increasing number of deaths by poisoning, once again emphasising "that barbiturates are the most prominent group of drugs causing these deaths." How great the increase has been in recent years can be seen from the latest available figures, which show that 75% of suicidal deaths due to drugs and 80% of all accidental deaths by poisoning are caused by barbiturates. From these facts it is evident, the article concludes, that the barbiturates present a hazard that the existing precautions against overdosing have not overcome and that "*the increasing number of these deaths would suggest that something more is needed.*"

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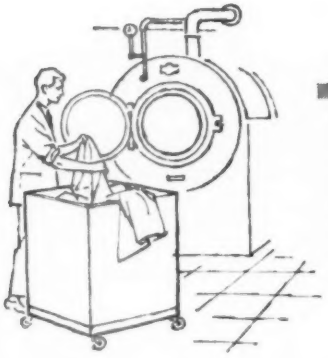

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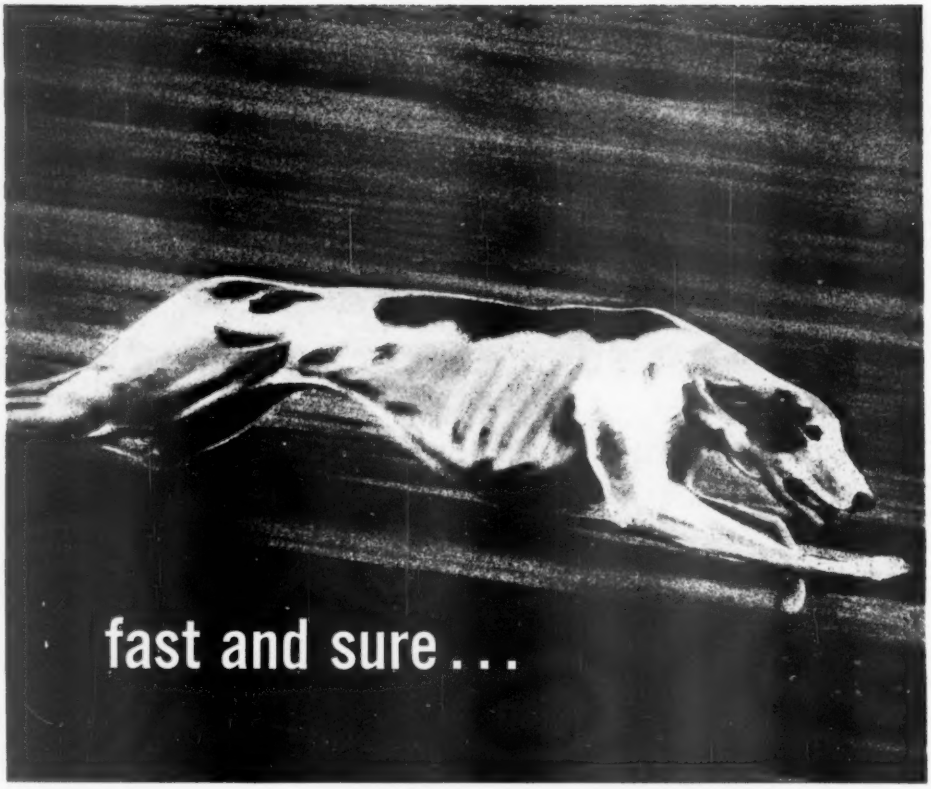

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Proceedings of the Royal Society of Medicine Vol. 53
1

Royal Society of Medicine

President—Sir GEOFFREY MARSHALL, K.C.V.O., M.D.

Meeting
October 12, 1959

NUFFIELD LECTURE[1]

A Great Benefaction

By Sir CLEMENT PRICE THOMAS, K.C.V.O., F.R.C.S.

IT is a great privilege to have been chosen to give this, the first Nuffield Lecture, although I feel that there are many others better fitted to do it. I think it is perhaps fitting that I should first make quite clear the way in which this Lecture originated.

On the occasion of Lord Nuffield's 80th birthday, our profession was given the opportunity of showing its appreciation for all that he has done to support the advancement of medical knowledge. The response came from all branches of our profession and from a gratifyingly large percentage of its members here and throughout the Commonwealth. The proceeds of the appeal were presented to Lord Nuffield with a personal gift to mark the occasion, and it was then decided by him, with his characteristic flair and generosity, that a lectureship should be established, through which any topic of current medical interest could be brought before the general medical public.

Lord Nuffield vested this Lecture in the Royal Society of Medicine, as being a body in which all branches of medicine in its widest sense are represented, thus ensuring that no facet of our profession is excluded. In this way, the Lecture can be said to have been founded to do honour to this great man, for that was the intention of those who responded to the original appeal. I have no doubt that in the future this Lecture will rank amongst those which already exist as a most important instrument in the dissemination of medical knowledge.

Lord Nuffield has received so many manifestations of the respect and affection in which he is held, that the detailed enumeration of them would make a long tale. Honoured by his sovereign with, first a baronetcy, then a barony, and finally a viscountcy, he received in 1917 the O.B.E., and in 1941 was created a G.B.E., and more recently he was made a Companion of Honour. He has received honorary degrees and diplomas from a dozen or more universities and colleges, and has been similarly honoured by innumerable scientific bodies, the most significant of these being his election to the Fellowship of the Royal Society. In this category, we are very proud to be able to count him as one of the Honorary Fellows of our Society. Not least amongst the honours conferred on him have been the Freedom of a number of towns and cities which have benefited from the wisdom and generosity of his benefactions.

I think it is only right and proper that in this first Nuffield Lecture, for the future record, a brief outline should be given of the career and benefactions of him we would delight to honour; these remarks being addressed to my medical audience. I then propose, very briefly, for the benefit of Lord Nuffield, to outline some of the advances made in those spheres of medicine which he has made his particular interest.

I have deliberately omitted reference to internal medicine, and also to the vast fields of chemical and physical biological research, for these are subjects with which I am but casually acquainted.

There are, of course, so very many facets to the career of one who has led such a busy and

[1]The Lecture was delivered in the presence of Lord Nuffield, and of the President and Members of the Council of the Society.

active life, that to compass them all, not only would be beyond my competence, but were it within it, there would not be sufficient time to deal with them adequately; in consequence, I can only touch on certain aspects.

Firstly, consider his technical skill, for this surely was the firm foundation on which the success of the whole Nuffield Organization was built, this skill coupled with his phenomenal business acumen.

It is true to say that his urge as a young adolescent was to be a surgeon, and there can be no doubt that his manual dexterity alone would have ensured his being ranked as a technical surgeon of the highest order; this was not to be, and there is no question that the greater good has resulted from this failure to have his wish granted, for, without doubt, many more people have benefited in so many ways as a result of his active support of the advancement of medical knowledge. It surely is granted to few individual surgeons to be able to confer the benefit of healing on as many of his fellow beings as those who can thank Lord Nuffield for such relief.

It is common knowledge that Lord Nuffield started life in a cycle-repairing business with the enormous capital of £4 sterling, but also with something worth more than money, his technical skill and the will to success. This latter led to a willingness to work all hours, early and late, also to the sacrifice of any temporary advantage in order to secure ultimate success. Very early in his career, his name came before the public eye in Oxford as being the means by which the *Oxford Times* was enabled to appear on its publication date. An essential cast-iron part of the linotype machine was fractured; no spare parts were available as the machine was so old. Young Morris offered to try to mend the part by brazing it, a manœuvre thought to be impossible at the time, so he was laughed to scorn. However, *faute de mieux*, they allowed him to try; the result, the part was returned in four hours, mended, and remained in service for nearly thirty years longer, in fact, until the whole machine was scrapped. The charge for the repair was a mere twelve shillings and sixpence.

One other story serves to show the man. He was charged to buy and deliver a motor-car to a client in Stirling in January 1906. He bought the car in Paris and took it to Stirling. The whole journey, apart from the Channel crossing, had perforce to be done by road, and this in the most miserable of wet cold weather. The journey took eleven days, and during this time there were no fewer than five major breakdowns, needing engineering reconstructions, which were carried out either on the roadside or in a village blacksmith's shop. The car was delivered by him, despite the fact that he was out of pocket on the transaction; he gained, however, experience and it allowed him justifiably to boast that he could get any car to the end of its journey.

The use of his hands has always had, and still has, a fascination for him; he worked himself in the shops until 1914, and even now he has tools and a lathe in his own home, and nothing gives him greater pleasure than to work with them.

It is often said of successful men that, of course, they were born at the right time, and in certain respects this could be said of Lord Nuffield, as long as one also postulates that any time would have been the right time for him. When he was starting in business for himself, there were a number of businesses in the same or allied fields in Oxford. If anyone had been asked to forecast at that time, on economic grounds, which of them was most likely to establish a large motoring organization in such an unlikely place as Oxford then must have seemed to be, it is most probable that one of the others would have been chosen. They all had equal opportunity, but there was only one William Morris.

His success in business must surely have rested on the following qualities: absolute integrity, imagination, courage, the ability to sacrifice an immediate advantage for a distant goal, tireless energy and the ability to get the best out of those associated with him.

Those who wish may read a detailed account of the growth from such small beginnings of the great Nuffield Organization

in "The Life of Lord Nuffield" by P. W. S. Andrews and Elizabeth Brunner (Oxford, 1955), to which I am indebted for a large amount of my information. The growth of his business depended a great deal on his practice in the early years of ploughing back into his concerns practically all the profits which accrued. This practice laid him open to the risk of serious financial stringency in the prosecution of his business affairs. It was in this wise: the Special Commissioners for Inland Revenue took action against him to recover super-tax on all the profits thus put back. The legal implications of the matter are too complex for me even to understand. The upshot, however, was that Lord Nuffield won his appeal against the decision and no action was taken.

Sir William Morris, as he then was, summed up his attitude to the accrued profits as follows: "In general terms, it has been my aim and object all my life to develop these businesses, and not to make money for myself; and, in so far as I have been able, to assist in the development of British manufacture and industry." He rightly pointed out later that if the avoidance of paying super-tax had been his aim and object, this could have been easily done by forming a company in a foreign country, an act contrary to all his principles. This combination of a shrewd business instinct and a fundamental integrity is the hall-mark of the man.

Even at the time when he was busiest with his own affairs, he was always able to look at the wider field and to appreciate the larger implications. In 1930, he became concerned about all the factors bedevilling labour relationships. He always was, and still is, a staunch believer in the British Working Man, and felt that there should be some method of circumventing these difficulties. In consequence, he was largely instrumental in forming the League of Industry, of which he was the first President. This was a non-political organization, in which people from all the political parties and representatives of all shades of industrial opinion served. Among other objects of the League, the following are, in my opinion, the most noteworthy:

(1) The creation between employers and the employed of a spirit of co-operation, so as jointly to promote and further any proposals for the improvement of their respective industries *and* the general industry of the nation.

(2) To maintain an organization, free from all sectional control and influence, whose

FIG. 1.—The Nuffield Medal. Designed by Mr. T. H. Paget, O.B.E.

object shall be, in general, and in the widest possible sense, to watch over the interest of all those engaged in industry, including agriculture and commerce as a whole.

I fancy I can detect the Nuffield imprint here, and how much better things would be if that vision were a reality. The passing of a world depression with its increase in trade led to a return to the party political line, and thus a great adventure in understanding came to an end.

Faced with a crisis in his own business in 1921, resulting from the immediate post-war slump, his reaction was typical. The sale of motor-cars decreased month by month until it became a mere trickle. Meanwhile, his factory premises and all available space were being filled with completed cars and, mark you, this was not the case at the Morris factories only. Other manufacturers were in like state. At this juncture he decided, contrary to the advice of all his sales staff, to decrease the price of the cars by £100, and this when the original profit on each car was only £15. Disaster was forecast; but no, the result was the breaking down of the deadlock, and the beginning of the end of the slump. There is no doubt that this courageous move saved many businesses which otherwise would have tottered into bankruptcy.

In the depression of the late 'twenties, when certain areas of the country, especially the mining areas, earned the desolate title of Depressed Areas, he deliberately embarked on an attempt to mitigate the effects of this depression by buying a coal-mine in the Forest of Dean, in order to give employment, and also with the idea of introducing modern methods into coal-mining. He was ill-advised about this particular colliery, and, in consequence, the venture failed. This, however, does not detract from his intention; who can tell but that, with sound advice on matters beyond his experience, the coal industry of the country might not have climbed out of the Slough of Despond much earlier than it did?

His interest was aroused, doubtless by this adventure, in the problem of the Special Areas, as these came to be called, in deference to the proud people living in them. Anyone who visited these areas during this time will not readily forget the gaunt men, clean and tidy in their threadbare clothes, standing idly at street corners, doing their best to disguise the look of hopelessness and despair on their faces, and the even gaunter women who lived on the edge of starvation so that their children should not want.

Lord Nuffield saw these things and pierced the mask, and as a consequence, in 1930, he started a fund of £2 million for these areas. This was to help finance new industries in the areas by loans to industry; how well this scheme has worked is manifest by the fact that all of these loans have now been repaid. Those who know the Special Areas, those villages, for example, which were wholly dependent on coal, which now have subsidiary industries, will appreciate fully the boon conferred on those communities, which no longer feel neglected.

The story of all Lord Nuffield's benefactions which must amount to approximately £30 million sterling is too long a tale for me to tell, even had I the time and were I able to do so. It should suffice a medical audience to say that there is scarcely a branch of medicine or its allied professions that has not received some benefaction from his gracious hand.

He had a specific reason for the majority of his benefactions, and before they were implemented, he gave as much care and attention as he gave to the managing of his business concerns, and sought expert advice in their implementation. Occasionally, however, he acted on the spur of the moment, as, for example, when he was returning from a trip to Australia. When his ship arrived in Fiji, he was met at the boat by the Governor's secretary with an invitation to luncheon at Government House, where he was placed next to the bishop. It was not until he arrived back at the boat that he realized that he had not only had a pleasant luncheon party, but that he had also promised to build a cathedral for the bishop.

His earliest benefactions were to the

University of Oxford, for the foundation of a Postgraduate School of Medicine, where Chairs in Medicine, Surgery, Obstetrics and Gynæcology, Anæsthesia, Orthopædic Surgery and Plastic Surgery have been founded. Since then, his medical benefactions have been too numerous to detail. I would like, however, to draw attention to certain of them that have had more than just local implication.

The outstanding, of course, is the Nuffield Foundation, which, in its continuance, will constantly influence so many aspects of health and general well-being. Its objects briefly are (1) the advancement of health and the prevention of illness by medical research, teaching and the development of medical and health services, (2) the advancement of social well-being, (3) the care of the aged poor, (4) the advancement of education, and (5) such other charitable purposes as shall be declared in writing by (*a*) Lord Nuffield, and (*b*) later by all the ordinary and managing trustees.

This, of course, is a wide platform from which a host of good works can be assisted.

The care of the aged poor was very close to the heart of the late Lady Nuffield, whose passing away, I know, was a very sad and irreparable loss to Lord Nuffield, a loss with which we have the deepest sympathy.

Lady Nuffield founded the Elizabeth Nuffield Home for Elderly Ladies, which is now administered by the Trust. Only recently, the President of the Nuffield distributors in America started a fund to help support this Home as a token of their sympathy and as a mark of respect and affection.

The Provincial Hospitals Trust was founded by him, and does for these hospitals what the King Edward VII Fund does for the London Hospitals. It also provides a fund for many things not normally budgeted for. It was through the Trust that Sir Howard Florey was financed to enable him to perfect the isolation of penicillin and initiate its clinical application.

The British United Provident Association owes its origin to Lord Nuffield. He, in fact, underwrote it at the outset, although now it is entirely self-supporting; it is still called by many the Nuffield Scheme, and what a boon it has been to so many.

One other benefaction needs mention, if only for the spirit which underlay its inception; that is, the provision of the Bolt respirators to hospitals. Seeing a headline in a paper one evening, that an iron lung had arrived too late to save the patient's life, he asked one of his friends, "If I distribute such lungs among the hospitals, would it save two lives a year?" On receiving the affirmative, he set the wheels in motion, and actually distributed 1,700 such respirators. The effort was worth while as far as he was concerned, provided that there was a chance of saving two lives.

I have surely said enough to indicate, if only imperfectly, the manner of man we wish to honour. Now let me briefly consider some of the outstanding advances made in the fields in which he was most interested.

One of his first medical interests was anæsthesia, and it is noteworthy that through his insistence alone, the first professorial chair in anæsthesia was established in this country, with Robert Macintosh as its first incumbent. The revolution in anæsthesia, since that time, has been quite remarkable. The anæsthetist of to-day is not merely a technician who keeps a patient unconscious for a sufficient time for a given operation; he is, at the same time, physician, physiologist and pharmacologist. Many advances in our knowledge of respiratory physiology have come through the field of anæsthesia; the modern approach to the poliomyelitic patient stems almost wholly from anæsthetic departments; the practical application of the ganglion-blocking agents, such as curare and other reagents producing muscular relaxation, and the use of the methonium compounds in the control of blood pressure, in order to minimize blood loss and facilitate certain operative procedures, have also been developed in these departments.

Similarly of late, they have been, and still are, playing their part in the field of hypo-

thermia, exploring its possibilities and trying to understand the physiological changes which occur in the hypothermic state.

These advances in anæsthesia have made an incalculable contribution to the increased safety and the extension of the limits of surgical intervention. Before such advances, it was necessary to resort to local anæsthesia in order safely to increase the length of time available for an operation; in thoracic surgery, for example, in the early 'thirties with the type of general anæsthesia then available, any operation on a patient over 50, which lasted more than one and a quarter hours, was fraught with great danger; hence the type of surgery was crude, even if effective. The whole picture changed with the advent of assisted respiration, introduced by Magill in this country, and by Crafoord in Stockholm; the latter showed conclusively that in the old-fashioned over-pressure method, the fatality was due to carbon dioxide retention. Anæsthesia now became safe and, with the introduction of adequate blood transfusion, definitive anatomical dissection became possible, the time the operation lasted became of relatively little importance, and the patient's condition at the end of the operation was little different from that at its start.

This physiological and pharmacological approach to anæsthesia has, of course, influenced the whole field of surgery, and has in large measure taken away from the patient the terror of an operation.

The comparatively new field of hypothermia is likewise opening up new vistas. By slowing down the basal metabolism of the body, it becomes possible to arrest the circulation either to certain organs, or to the whole body, for periods of up to or even exceeding forty-five minutes, depending on the level to which the body temperature is lowered. This allows of surgery on the open dry heart, surgery for the relief of carotid artery thrombosis, and doubtless, in the future, for any surgical intervention which calls for either general or local circulatory arrest; one day, without doubt, the difficult problem of coronary artery occlusion will be overcome by its use.

Orthopædic surgery, born, one might almost say, in the 1914–18 war, the child of Robert Jones, became one of Lord Nuffield's especial interests, which he expressed in the foundation of a Chair in Orthopædics at Oxford. Almost at the same time, the small Wingfield Hospital was enlarged to house the department, with G. R. Girdlestone as its first Director and Professor. Simultaneously, endowments for orthopædics were made in both Australia and South Africa.

Since 1930, probably the outstanding advances in orthopædics have been mainly in the field of fractures and that of the paralytic diseases. The discovery and use of inert metals for the internal fixation of fractures is possibly one of the greatest advances in the orthopædic surgery of this era. Reflection on the complications attendant on the use of the old-fashioned plates and screws with the inevitable necroses and rarefaction occurring around them necessitating their removal, makes a striking contrast with present-day practice. The absence of reaction to those metals used at the present time allows them to be left *in situ* indefinitely. The two outstanding procedures introduced since that time have been nailing of fractures of the neck of the femur, and intramedullary nailing of complicated long-bone fractures. The former has not only made life more tolerable for the elderly patients, but has been the most important factor in saving their lives, for, in a large percentage of cases, rapid mobilization and also rapid union are achieved. Such fractures are now relatively simple to treat, whereas previously they were a constant source of anxiety.

The other outstanding advance has been the management of flail limbs and joints by arthrodesis, thus fixing the joints and, in the lower limb, giving the patient a stable limb on which to walk.

It is also noteworthy that congenital deformities now are treated more by early mechanical correction than by operation. The group of talipes is treated from birth by manual correction and light splinting at a time when they can be corrected. Similarly, the poliomyelitic paralyses are treated early,

and, by re-education, the portions of muscle still functioning are taught to take on the function of the whole. Tendon transplant, although still used, is not indicated with anything like the frequency it was in the 'twenties and early 'thirties. The whole problem of rehabilitation of the orthopædic case has done as much as the surgery itself to lead to success.

In neurosurgery, the chief interest of the first Professor of Surgery at Oxford, the late Hugh Cairns, there have been some striking advances. The success of the early surgical attack on the ruptured berry aneurysm is notable. This success depends on another advance, angiography, which appropriately enough was first used in neurosurgery.

Angiography has since been used in many fields, in cardiac surgery, in that of peripheral vascular disease, and in the diagnosis of tumours in various organs; incidentally, the original purpose of angiography was for the diagnosis of tumours of the brain. Its use has been either general or selective, and the introduction of vascular catheterization has made selective angiography possible in areas hitherto inaccessible, as, for example, the kidney.

Two other interventions are noteworthy. Firstly, the removal of clot from the brain after a large cerebral hæmorrhage. Secondly, removal of a whole cerebral hemisphere in cases of otherwise uncontrollable athetoses. Both these operations are indicated only rarely but, when they are successful, give dramatic results.

Plastic surgery engaged the attention of Lord Nuffield when he heard of the burns, particularly those occurring in tanks, in North Africa. As a result, a Chair in Plastic Surgery was established in the University of Oxford, the first one in this country, which undoubtedly afforded great stimulus to the work; it is sad to relate that on the retirement of Professor T. P. Kilner, the Chair has been allowed to lapse.

The greatest advance in plastic surgery has been in the treatment of burns. The secret of advance was the appreciation of the cause of fatality in the loss of fluid and protein, and that its rectification lay in fluid and protein replacement and the prevention of further loss by early skin grafting. Burns involving large body areas, as occurred not infrequently during the last war, gave rise to difficulty in finding sufficient area of donor sites to cover the affected area with autogenous grafts, and perhaps the greatest advance was the use of homologous grafts alternating in strips with autogenous ones. This provided cover for three to four weeks for the whole area, and by that time, the patient's own donor areas could often be used again. This raised the question of rendering the homologous graft acceptable to the host; this has been achieved to some extent in small animals, and when it can be done in man skin banks can be established. Its achievement, however, would open up other vistas, for it means that once the antigenic action of a homologous graft can be overcome, then organ grafts, such as kidney and liver, may become possible, bringing doubtless many difficult questions in their train.

One of Lord Nuffield's early interests was in obstetrics, and one of the first Oxford Chairs was in Obstetrics and Gynæcology, with Chassar Moir as the first Professor.

Broadly speaking, the greatest advance in obstetrics has been the appreciation of its importance by, not only the profession, but also the general public. This has led to the establishment of antenatal and postnatal clinics, within easy reach of practically every woman in the country. Similarly, there has been an increase in the number of hospital beds devoted to obstetrics, so that practically every woman can be admitted to hospital at least for her first baby.

Another great advance in obstetrics has been the almost complete eradication of puerperal sepsis, whereby maternal mortality has been reduced more than fivefold. Proper antenatal and postnatal care, appreciation of the dangers of over-examination and, latterly, the introduction of chemotherapy and antibiotics have been largely responsible for this advance.

The introduction of the operation of lower segment Cæsarean section has also been a

great boon, in that operation can be undertaken after labour has started while also making possible repeated Cæsarean sections. One other observation of importance is the recognition of the Rhesus factor in the blood. It can now be forecast with reasonable accuracy whether or not the child will be affected in such cases, and when such a situation arises, the ill-effect on the child can be, to a large extent, overcome by replacement transfusion.

Dentistry was one of Lord Nuffield's interests and as with his other benefactions, he sought advice as to the best method of implementing this one. The crying need at this time was for well-trained dentists and this necessitated the existence of an adequate academic corps which would undertake their training. His advisers were well aware of the different needs of medical and dental students, especially so in the basic sciences; in consequence of this, it was decided that rather than try to adapt the dental curriculum to suit the existing course, a course should be devised to suit the requirements of the dental student. In consequence, it was decided that gifted students, at the end of their ordinary course in anatomy and physiology, should be encouraged to do an honours course in these subjects together with biochemistry, provided that on finishing their dental course, they had the intention of taking up an academic career. Alternatively, travelling fellowships were, and are, granted in dentistry, medicine, or science, to young dental graduates, which are tenable in schools either in this country or in America or Scandinavia. Both of these schemes have been financed by a Nuffield benefaction, and as a result there has been built up in this country an academic corps which previously did not exist. This now affords a sound basis for a comprehensive dental education of which we may be justly proud. Latterly Lord Nuffield has endowed a Nuffield Chair in Dental Research in the Faculty of Dental Surgery of the Royal College of Surgeons; the first fruits, I am assured, can already be seen.

I have tried, though not as well as I would have wished, to give you a picture of the man we wish to honour, and of his benefactions and some of the benefits in the field of medicine that have accrued from them. I am fully aware that many influences outside the scope of these benefactions have contributed to, and in some cases initiated, the advances I have tried to indicate, but nothing can detract from the overall picture of an astounding benefaction. The integrity and vision, not to mention the generosity of outlook and actions of Lord Nuffield, will for ever remain a striking example for all those who have at heart the welfare of their fellow beings.

For all these things we honour and respect Lord Nuffield; our affection, however, is commanded by something equally precious, his humanity and modesty. Who, having met him, can forget the warm interest he evinces in those around him? Those who know him can vouch for a host of generous acts which have scarcely seen the light of day.

Sir, I hope that to-day, through me, you will accept from our profession a gratitude and affection which is much warmer than any words of mine can express.

Linoleic-rich Dietary Fat

While linoleic-rich (vegetable oil) diets are believed by some authorities to have possible value in the treatment or avoidance of ischaemic heart troubles, medical opinion has been, and still is, sharply divided about the causes of coronary diseases.

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Proceedings of the Royal Society of Medicine Vol. 53 9

Royal Society of Medicine

President—Sir GEOFFREY MARSHALL, K.C.V.O., M.D.

Meeting
October 29, 1959

SYMPOSIUM ON ATHEROSCLEROSIS

SECTION I

Chairman—Professor G. PAYLING WRIGHT, D.M.

Some Aspects of the Pathology of Atherosclerosis

By Professor T. CRAWFORD, M.D., F.R.F.P.S.

London

THE essential nature and cause of atherosclerosis being undetermined, the only definition which I can give to introduce the subject of this Symposium must be a descriptive one. On this basis atherosclerosis can be defined as the widely prevalent arterial lesion characterized by patchy thickening of the intima, the thickenings comprising accumulations of fat and layers of collagen-like fibres, both being present in widely varying proportions.

Though leaving much unsaid, this definition contains the three key points which distinguish atherosclerosis from other forms of arterial lesion: first that the lesions are mainly intimal; second, that they are patchy; and third, that both fat and fibrous strands enter into their make-up.

The early lesions.—The earliest lesions which the pathologist can perceive on examining the intimal surface of a minimally affected artery are tiny gelatinous droplets, just visible with a hand lens. Microscopically all that can be seen is some loosening of texture of the intima, with increase in the amount of metachromatic ground substance between the fibres, but if an adjacent section is stained for fat numerous sudanophil droplets are seen scattered through the tissue.

Rather more advanced are the lesions usually called fatty streaks, which are slightly elevated yellow lines running longitudinally in the intima. They are seen particularly well on the posterior wall of the aorta and in the common carotid arteries.

Microscopically (Fig. 1) these lesions consist of clusters of fat-filled histiocytes lying immediately under the endothelial cell layer. The appearances suggest that the fatty droplets seen in the earlier lesion have now been swept up by the histiocytes, but why the cells should become arranged into streaks in this way remains unanswered.

The fate of fatty streaks.—Although it is impossible to obtain direct evidence, circum-

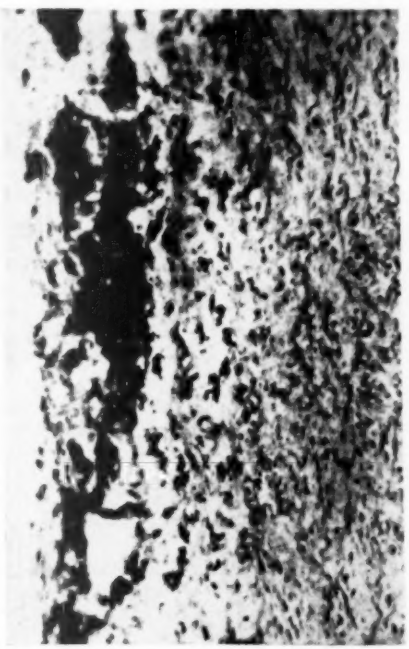

FIG. 1.—Longitudinal frozen section of a fatty streak from the aorta, showing clusters of fat-filled (dark staining) histiocytes in the superficial layers of the intima. Stained Sudan III and hæmatoxylin × 175.

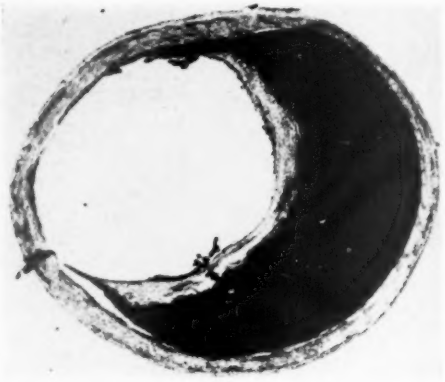

FIG. 2.—Transverse frozen section of a coronary artery, showing atheromatous plaque consisting almost entirely of fat with very little of the fibrous element. Stained Sudan III and hæmatoxylin. × 15.

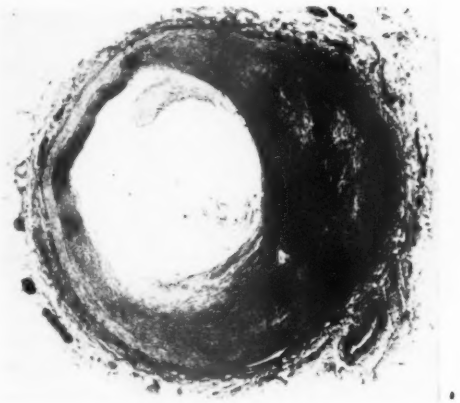

FIG. 3.—Transverse section of a coronary artery, showing an atherosclerotic area in which there is predominance of the fibrous element. Weigert-van Gieson stain. × 15.

stantial evidence suggests that fatty streaks are reversible. Indeed it seems probable that during early life they develop and disperse regularly in the intima of the larger arteries. There may be a cyclical accumulation and utilization of fats in the intima in response to factors of which we know nothing—but this is pure conjecture.

Not all workers in this field would agree that these fatty streaks contain the seeds of atheromatous plaques. It seems to me, however, that they are the likely starting points for the more significant lesions and that at certain foci something interferes with dispersal of the fat, which increases in amount until ultimately a point of no return is reached. This conversion of the fatty streak into the atheromatous plaque requires not only focal increase in the amount of fat, but in addition the development of a fibrous layer separating the fat from the lumen. The use of an extremely sensitive technique for the identification of fibrin (Crawford and Woolf, 1960) employing a fluorescein-coupled specific antibody to human fibrin has enabled my colleague Dr. N. Woolf to show that many fatty streaks have, even from an early stage, delicate strands of fibrin overlying the surface and lying between the layers of histiocytes. The suggested explanation is that the fibrous layers which separate the fat from the lumen in even quite small lesions are formed by deposition of fibrin, due perhaps to interference with the functions of the endothelial cells, the integrity of which is of so much importance in maintaining the fluidity of the blood.

Features of the advanced lesions.—Sometimes the predominant feature is increase in the amount of fat (atherosis) with relatively much less production of the fibrous element. The result is then the characteristic yellow plaque, giving the signet-ring deformity to the lumen of the emptied vessel, to which the name atheroma is most aptly applied (Fig. 2). At other times the sclerotic element predominates and there is great fibrous thickening of the intima with much less conspicuous—but never absent—fatty accumulations (Fig. 3). It is to this fully developed stage that the term atherosclerosis is most appropriate, though it is now commonly employed for the whole series of lesions.

Calcification may occur at any time, but is generally most conspicuous in older subjects, and therefore presumably in the older lesions. It is usually confined to the intima, where it commonly starts at the periphery of fatty accumulations, but may spread to become very extensive. This intimal calcification in atherosclerosis is to be clearly distinguished from calcification of the media (Mönckeberg's sclerosis), a quite distinct condition which may occur in the absence of intimal disease.

The thrombogenic hypothesis.—In 1946 Duguid, studying serial sections of stenosed coronary arteries, observed transitions between obvious organizing thrombi and atheromatous plaques. He suggested that many of the lesions classified as atherosclerosis are arterial thrombi which, by the ordinary process of organization, have been transformed into fibrous thickenings. He added that many of the atheromatous fatty patches resulted from softening occurring in the thrombi.

Duguid's observations have not lacked confirmation (Crawford and Levene, 1952; Morgan, 1956) and few would now deny that the incorporation of mural thrombi is one factor—perhaps the main factor—leading to fibrous thickening of the intima.

Delicate fibrinous incrustations are easily found on the arterial intima and their mode of incorporation is of interest. They are rapidly covered and also permeated by endothelial cells extending in from their margins, and it is these cells, supported by oxygen and nutriment diffusing from the blood in the lumen, which are responsible for organization of the superficial parts of the thrombus. Indeed, if the deposit is a thin one it will be organized throughout in this way; but with thicker deposits, or when successive thrombi are superimposed at the same site, the layers farthest from the lumen are organized by extension through the media of capillaries from the vasa vasorum. Failure of these two zones of organization to link up sometimes occurs leaving a zone of softened debris rich in fats.

Vascularization of the intima.—I have stressed this mechanism for the organization of mural thrombi because, as a result, the normally avascular intima becomes richly vascularized. Most of the vessels reach it from the vasa vasorum (Fig. 4), but there may be an occasional abnormal capillary entering from the lumen (Fig. 5).

This intimal vascularization has been widely blamed for certain subsequent events in the natural history of atherosclerosis. Hæmorrhage from these capillaries into the atheromatous plaque has been held responsible for arterial occlusion (Paterson, 1936, 1938) either by enlarging the plaque to compress the lumen or by initiating thrombosis over the plaque. It seems to me, however, impossible that blood escaping from capillaries could build up sufficient force to compress the arterial lumen in which the pressure is much higher; and little evidence of this occurrence has been seen in the many occluded arteries I have examined. When bulky hæmorrhages are found enlarging the plaque they are likely to have followed cutting off of the pressure in the arterial lumen. The initiation of thrombosis by diffusion of breakdown products from an area of hæmorrhage is a possibility that has not been confirmed.

Secondly, some workers have maintained that repeated small hæmorrhages from these intimal

FIG. 4.—Base of atherosclerotic plaque, showing capillaries erupting from the media on the right into the intima on the left. Stained H. and E. × 160.

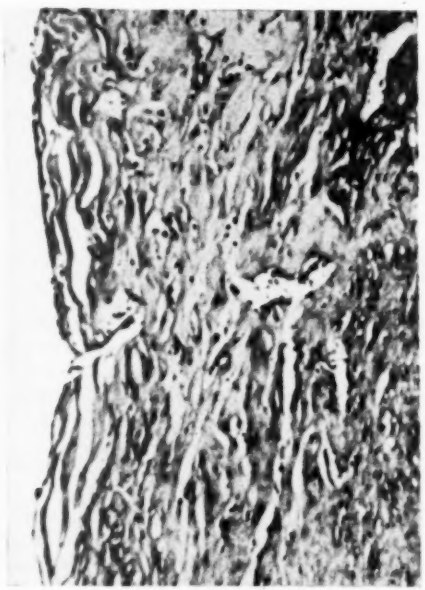

FIG. 5.—Atherosclerotic aorta showing capillaries extending into the intima from the lumen. Picro-Mallory stain. × 150.

FIG. 6.—Atheromatous plaque in a coronary artery, showing thinning of the media and disintegration of the internal elastic lamina at the base of the plaque. Stained H. and E. × 40.

capillaries are the source of the fat in the atherosclerotic region (Morgan, 1956; Paterson *et al.*, 1956; Duguid and Robertson, 1957). While it may be that fat is contributed to the lesion in this way, it can scarcely be the main source because sometimes enormous accumulations of fat occur before intimal vascularization is established. The claim by Paterson *et al.* (1957) to have demonstrated capillaries in the earliest lesions by alkaline phosphatase staining is unconvincing.

Alternative views on the source of the fat are: (*a*) The imbibition theory (Aschoff, 1924) assumes the penetration of plasma lipids into the intima by direct pressure filtration. (*b*) The origin of fat from softening of incorporated thrombi is an integral part of the thrombogenic hypothesis outlined above. (*c*) The origin of fat from degenerating elastic tissue recently discussed by Adams (1959).

The probability is that more than one of these mechanisms—perhaps even all of them—may contribute fat to atherosclerotic lesions, but the appearances in the earlier and in the more purely fatty lesions are most easily explained by the imbibition theory.

Medial changes.—Although atherosclerosis is defined in terms of the characteristic intimal changes, there are always associated structural changes in the media (Crawford and Levene, 1953). These may consist of no more than a trivial degree of medial thinning, but in severely affected segments the media may be almost completely lost and in addition the internal elastic lamina may completely disintegrate over considerable stretches of the vessel wall (Fig. 6). Occasionally the fatty accumulations, characteristically confined to the intima, also extend to involve the media.

Effects on the calibre of the lumen.—One of the most extraordinary things about atherosclerosis is its unpredictable effect on the calibre of the affected arteries. Paradoxically this single disease may leave the calibre unchanged—perhaps the commonest effect; or it may lead to severe stenosis, progressing to complete occlusion—most often in the coronary arteries, but also in the arteries of the leg, and in the vertebral, internal carotid and middle cerebral arteries; or finally the affected vessel may undergo dilatation, characteristically at the lower end of the aorta, where it produces what is now the commonest variety of true aortic aneurysm, but also at times seen in the basilar and even the coronary arteries. The particular effect in any given instance depends on the balance between a number of factors, including the blood pressure, the degree of medial damage, the rate of thrombus deposition and incorporation, and the external support available for the vessel wall.

In concluding this brief pathological introduction to the Symposium I would like to stress the error of looking on atherosclerosis as a static condition of the vessel walls: morphological studies all point to a constant state of flux in the lesions with variations in the amount and distribution of lipids, deposition and incorporation of fibrin, intimal vascularization and sclerosis all proceeding side by side. It is indeed this state of plasticity which gives some hope of influencing the course of the disease.

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A Series of Electron Micrographs of the Intima of Blood Vessels

By Professor Sir HOWARD FLOREY, F.R.C.P., F.R.S.
Oxford

PROFESSOR FLOREY showed some electron micrographs to display some of the features that can be recognized in the endothelium of a capillary in striated muscle. The basement membrane, the caveolæ and vesicles, and the intercellular junctions with their adhesion plates were pointed out (Figs. 1 and 2). It was shown that such endothelial cells also contain the usual cytological components, such as mitochondria, endoplasmic reticulum and the Golgi complex. The aortæ of rabbits and rats were shown to be lined by endothelium which resembled that of muscle capillaries in all essentials except that it was not possible to demonstrate a basement membrane (Figs. 3 and 4). In addition to the endothelial cells the intima of the aorta was seen to consist of collagen and elastic fibres. In some places cells lay in this tissue between the endothelium and the internal elastic lamina. It was pointed out that probably mucopolysaccharide exists in the spaces which are clear in an electron micrograph, since mucopolysaccharide

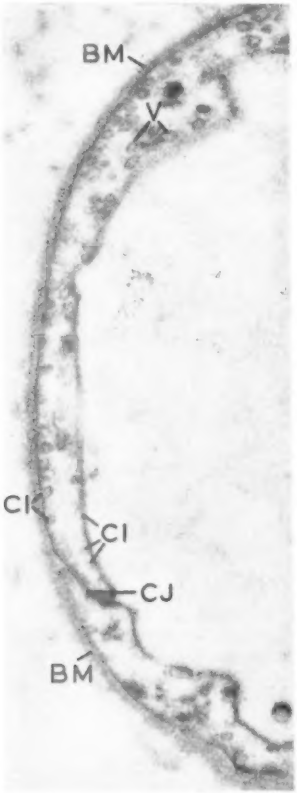

FIG. 1.—Normal capillary in muscle of rabbit tongue. BM—basement membrane. Note the gap where this crosses the junction between two cell borders (CJ). Caveolæ intracellulares (CI) are seen to abut on the internal and external surfaces of the endothelium. Intracellular vesicles (V) are also shown. × 32,700.

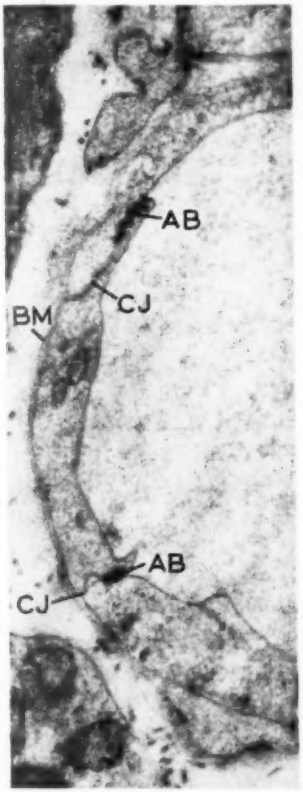

FIG. 2.—Capillary in muscle of rabbit tongue to show especially the electron dense areas at cell junctions (CJ). They have been called attachment belts (AB). BM—basement membrane. × 32,700.

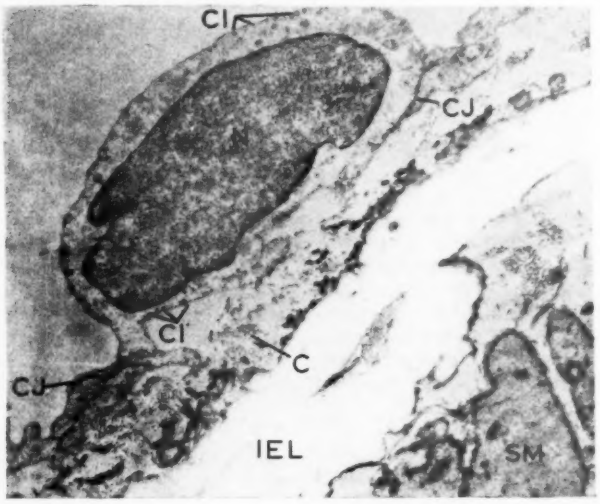

FIG. 3.—Normal rabbit aorta. N—nucleus of endothelial cell; CJ—cell junctions between neighbouring endothelial cells; CI—Caveolæ intracellulares similar to those in capillary endothelium; C—sections of collagen fibres; IEL—internal elastic lamina; SM—smooth muscle cell. Note that no basement membrane is visible at the internal surface of the endothelial cells. × 11,300.

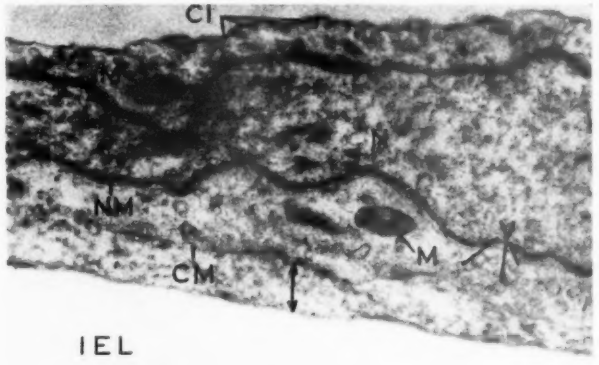

FIG. 4.—Normal rat aorta. N—nucleus of endothelial cell; NM—double nuclear membrane; CI—caveolæ intracellulares; V—intracellular vesicles; CM—cell membrane. Note that there is no definite basement membrane as in capillaries. ↕—space filled with amorphous material between cell and internal elastic lamina (IEL). × 26,000.

does not become electron opaque after osmium tetroxide fixation. In considering intimal lesions of arteries it is necessary to take into account the possibility that present methods may not be sufficiently delicate to detect the earliest changes. Any changes occurring in the subendothelial tissue may be secondary to changes in the endothelium, for it is through the lining endothelium that substances gain access to the inner two-thirds of large arteries. In attempting to pursue electron microscopic investigation of human material there is the very serious difficulty of getting adequately fixed material.

[For further details and illustrations, *see* Pathogenesis and Treatment of Occlusive Arterial Disease. Edited by Lawson McDonald. London; 1960 (in the press).]

Plasma Lipids and Atherosclerosis

By M. F. Oliver, M.D., F.R.C.P.Ed.
Edinburgh

In 1847 Vogel established that cholesterol was present in atheromatous plaques. Virchow (1856) suggested that these plaques were partly due to the passage of blood from the arterial lumen into the vessel wall and to subsequent fatty deposition. Since Anitschkow and Chalatow (1913) first produced atheroma in rabbits, it has been known that various diets, rich in cholesterol, result in the development of fairly typical atheromatous lesions in many different species. Such diets lead to atheromatous lesions only when they cause elevation of the plasma cholesterol level and usually the severity of the lesions can be directly related to the degree and the duration of hypercholesterolæmia. These observations have led to intensive study of the plasma lipids in patients with atherosclerosis.

Plasma Lipids

The principal plasma lipids are triglycerides or neutral fats (which can aggregate to form chylomicra), cholesterol and phospholipids. Triglycerides, most of the plasma cholesterol and all phospholipids are esterified with various fatty acids. The concentration of plasma triglycerides depends largely on the phase of intestinal absorption of fat, but the plasma cholesterol and phospholipid levels are independent of fat absorption. These lipids are transported in plasma combined with one another and with protein in macromolecular or lipoprotein complexes, some properties of which have recently been reviewed (Boyd and Oliver, 1958). These complexes can be fractionated according to certain chemical and physical characteristics into beta-lipoproteins (low density, or III–0 fraction) and alpha-lipoproteins (high density, or IV–1 fraction).

The plasma lipids currently estimated in investigations into atherosclerosis are triglycerides and chylomicra, total (esterified and unesterified) cholesterol, phospholipids, alpha- and beta-lipoproteins and their subdivisions and, more recently, the fatty acid composition of plasma and of ester cholesterol. In general, elevation of plasma cholesterol is associated with elevation of beta-lipoprotein cholesterol and often with reduction of alpha-lipoprotein cholesterol, and reduction of plasma cholesterol with the converse lipoprotein pattern. Since these are interdependent variables, it is permissible to simplify this discussion by considering particularly the concentration of total cholesterol in plasma in health and in relation to atherosclerosis.

Plasma Lipids in Health

In health the plasma cholesterol level is not constant but may fluctuate, for reasons largely unexplained, by as much as 20% (Levere *et al.*, 1958). In newborn infants the level is low but rises rapidly within the first ten days and thereafter gradually until puberty (Sperry, 1936). In men plasma cholesterol continues to rise slightly until about the middle thirties after which it remains fairly constant (Adlersberg *et al.*, 1956). In women there is a regular cyclical change with each menstrual cycle and plasma cholesterol may be 20% lower at the time of ovulation than during the preceding and succeeding weeks (Oliver and Boyd, 1953*a*). There is also a significant rise during the decade after the menopause (Oliver and Boyd, 1959*a*). The plasma cholesterol level also varies according to race, but it is difficult to dissociate primary racial influences from dietetic habits (Keys, 1956), and it is probable that racial differences are largely a function of nutrition which itself has an important effect.

All these factors which influence plasma lipid levels in health are important when assessing changes in lipid levels in relation to atherosclerosis.

Plasma Lipids in Coronary Heart Disease

Certain plasma lipids are often abnormal in patients with coronary heart disease. The plasma cholesterol and to a lesser extent the plasma phospholipids are both elevated; thus in many patients the cholesterol/phospholipid (C/P) ratio is also elevated (Gertler *et al.*, 1950; Steiner *et al.*, 1952; Oliver and Boyd, 1953*b*). The beta-lipoprotein cholesterol and certain low-density lipoproteins are frequently elevated (Barr *et al.*, 1951; Jones *et al.*, 1951; Nikkilä, 1953; Oliver and Boyd, 1955; Smith, 1957; Dodds and Mills, 1959). These abnormalities are not present in all cases but are more marked and more frequent in those under 50 years than in older patients. Dodds and Mills (1959) have clearly shown that significant changes also occur in the plasma lipoproteins during the first two months after an acute myocardial infarct.

After a meal additional fat, almost entirely in the form of chylomicra, enters the blood stream from the thoracic duct and causes a transient increase in triglycerides and visible lipæmia. In patients with coronary heart disease the duration of this postprandial lipæmia is longer than in healthy subjects (Becker *et al.*, 1949; Barritt,

1956), and near its peak it is less readily cleared by heparin (Block *et al.*, 1951; Oliver and Boyd, 1953*c*). Evidence that such persistence of chylomicra may favour blood coagulation has been fully reviewed by Poole (1958).

Because coronary atherosclerosis has in part been attributed to a dietetic deficiency of essential unsaturated fatty acids (Sinclair, 1956), measurements have been made of the plasma fatty acid composition in patients with coronary heart disease. Although Antonis (1957) reported a lower percentage of dienoic acids in coronary patients than in normal subjects, James *et al.* (1957), using gas liquid chromatography, could detect no significant abnormality in the fatty acid composition of serum. Whereas Lewis (1958) found a significantly lower percentage of linoleic and arachidonic acids in plasma ester cholesterol in coronary patients, Wright *et al.* (1959) did not find any difference in the essential fatty acid content of cholesterol esters of atheromatous tissue and of healthy aortas. Employing chromatographic separation of cholesterol esters by silicic acid columns, we have observed no difference in the fatty acids of ester cholesterol in patients with coronary disease and in healthy men, and the only significant finding is that the fatty acids appear less saturated in young women than in young men. More studies of fatty acid compositions are clearly required.

No definite abnormality of the plasma lipids has been established in patients presenting with cerebral or peripheral vascular disease. Many such patients have co-existing coronary atherosclerosis, often of an advanced degree, and any attempt to differentiate patients with atherosclerosis in one vascular system from those with atherosclerosis in another is likely to be misleading. Our investigations have indicated that the plasma lipid pattern in patients with predominant cerebral or peripheral vascular disease has the same trend as in coronary patients but is less abnormal.

Ætiological significance of abnormal plasma lipids.—The positive relationship between hypercholesterolæmia and the development of atheromatous lesions, established in many animals, probably also applies in man. Epidemiological studies in the United States indicate that there is an increased risk of coronary heart disease in individuals with antecedent elevation of plasma cholesterol (Dawber *et al.*, 1957; Doyle *et al.*, 1957). Familial hypercholesterolæmia, whether xanthomatosis is present or not, is also associated with increased susceptibility to coronary heart disease (Epstein *et al.*, 1959). Furthermore, the Co-operative Study of Lipoproteins (1956) has indicated that elevation of plasma cholesterol precedes the development of coronary heart disease and is not merely associated with the onset of clinical features.

There would seem to be four possible explanations for this association of coronary heart disease with a disturbance of plasma lipids.

(1) It might be a chance association, but this can be dismissed with reasonable confidence since many comprehensive investigations have indicated that a significant association exists.

(2) It is conceivable that a primary change within the wall of the coronary arteries could result in a disturbance of the plasma lipids. The arterial wall is capable of synthesizing cholesterol, and Werthessen *et al.* (1954) have suggested that in growing animals the arterial wall may supply cholesterol to the plasma. Since the liver is the most active organ in synthesizing cholesterol and arterial cholesterol biosynthesis decreases with age, this source of plasma cholesterol is probably not very important in relation to atherosclerosis. Nor is it likely that some primary mural lesion, such as capillary hæmorrhage or degenerative processes which may both be associated with accumulation of cholesterol esters, is capable of influencing the plasma lipids significantly. Moreover the quantity of lipid in atherosclerotic lesions is so large that it cannot all originate from the breakdown of arterial tissue (Duff and McMillan, 1951).

(3) Elevated plasma lipids may contribute directly towards the development of coronary atheroma. This is widely believed to be one ætiological factor, and the lipid composition of atherosclerotic plaques and of plasma is sufficiently similar to suggest that the lipids of the plaque are derived at least in part from the plasma. Isotope studies indicate that plasma cholesterol can be incorporated into atherosclerotic plaques in man.

(4) The association of abnormal plasma lipids and coronary heart disease might be secondary to other disturbances of physiological function. For example, deposition of fibrin on the arterial intima could act as a selective filter preventing the passage through the arterial wall of large lipoprotein molecules from the lumen and lead to disturbance of the plasma lipids. However, most of the exchanges between plasma and interstitial fluid which involve ultra-filtration and reabsorption of plasma components occur in the capillary bed, which is comparatively free from atherosclerosis. Another possibility is that alteration in the normal endocrine balance could lead to a disturbance of plasma lipids, of blood coagulation and fibrinolysis, of connective tissue and arteriolar permeability and thus to the development of atheroma (Oliver and Boyd, 1958).

Diagnostic significance of abnormal plasma lipids.—The diagnosis of coronary heart disease is, of course, based on clinical and electrocardiographic assessment and not on the finding of abnormal plasma lipids. The normal range of plasma lipids is wide and the abnormalities in coronary heart disease are slight. It is therefore seldom possible to attach diagnostic significance to an individual lipid pattern.

On the other hand, gross hypercholesterolæmia is probably a significant finding in a patient with equivocal clinical features. Most young males with coronary heart disease have abnormal plasma lipid levels. The percentage of coronary patients with "normal" values and the percentage of healthy subjects with elevated values are shown in Tables I and II. Under the age of 40,

TABLE I.—THE PERCENTAGE OF APPARENTLY HEALTHY ADULTS AND OF PATIENTS WITH CORONARY HEART DISEASE WITH "NORMAL" PLASMA LIPID LEVELS

	Healthy group		Coronary group			
Age groups	26–49	50–69	26–39	40–49	50–59	60–69
No. of cases ..	100	60	100	150	50	50
Mean age ..	39	59	37	46	54	64
"Normal" plasma cholesterol ..	83%	63%	11%	25%	38%	48%
"Normal" plasma cholesterol and "normal" C.P ratio ..	87%	68%	9%	21%	38%	44%

TABLE II.—THE PERCENTAGE OF APPARENTLY HEALTHY ADULTS AND OF PATIENTS WITH CORONARY HEART DISEASE WITH "NORMAL" LIPOPROTEIN LEVELS

	Healthy group		Coronary group		
Age groups ..	26–49	50–68	26–39	40–49	50–68
No. of cases ..	50	36	50	50	50
Mean age ..	40	58	37	45	57
"Normal" lipoprotein ratio	92%	72%	20%	34%	64%

less than 10% of the patients have a "normal" value for plasma cholesterol, cholesterol/phospholipid ratio, or alpha/beta lipoprotein ratio (Oliver, 1958). These particular values are only valid for the method and community under study, but do indicate that a normal plasma lipid pattern is seldom present in men who develop coronary heart disease in their thirties or early forties.

Therapeutic implications of abnormal plasma lipids.—Since hypercholesterolæmia is associated with an increased incidence of coronary heart disease, it is probably desirable to lower elevated plasma cholesterol levels, particularly in young subjects. As yet there is no convincing evidence that this has improved the prognosis, and preliminary observations suggest that the mortality from myocardial infarction has not been significantly improved by lowering plasma cholesterol (Oliver and Boyd, 1959*b*; Stamler *et al.*, 1959). This evidence is lacking largely because there have been insufficient and inadequately controlled studies of the effect of reduction of plasma cholesterol on prognosis. The rarity of atherosclerosis in concentration camp victims (Helweg-Larsen *et al.*, 1952) suggests that even advanced lesions may be reversible, but it would be surprising if a reduction of plasma cholesterol alone could make much difference to a sclerosed, fibrotic and often calcified arterial wall or to a fibrosed and relatively ischæmic myocardium. Ideally, the benefit of lowering the plasma cholesterol level should be tested over a five- or ten-year period in apparently healthy hypercholesterolæmic young men.

Summary

Although abnormal plasma lipid levels are found in many patients with coronary heart disease, the ætiological significance of the association of hypercholesterolæmia with human atherosclerosis has not been explained. Plasma lipid abnormalities are most marked in young men with coronary artery disease and in such patients may be a useful adjuvant to a difficult clinical diagnosis; in older patients they have little diagnostic significance. The desirability of correcting abnormal plasma lipid levels has not yet been established.

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Atherosclerosis of the Coronary Arteries—Epidemiological Considerations

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CORONARY heart disease is due mainly to complications of coronary atheroma, in which thrombus formation at the site of, hæmorrhage into, or breakdown of an atheromatous lesion occurs. The outstanding clinical and epidemiological feature is a higher incidence in males than in females, and an apparent increase of incidence in the last twenty to thirty years in this and other Western countries (Morris, 1951).

Geographical variation.—The mortality rates for Japanese in Japan, Hawaii and the U.S.A. suggest that "westernization" has induced a similar increase and a similar sex ratio (Table I).

TABLE I.—CORONARY HEART DISEASE: GEOGRAPHICAL VARIATION (Gordon, 1957, 1959; U.S. Dept. of Health, 1952; WHO 1955)
Mortality Rates Per Million. Japanese in U.S.A., Hawaii and Japan, 1949–52. Ages 45–64 Years

Sex	U.S.A.	Hawaii	Japan
Male	2,682	1,503	*900
Female	840	511	*790

*Arteriosclerotic and degenerative heart disease.

The implication of such changes in experience of one racial group, is that environmental factors may be of major importance. In support of this is the experience of Yemenite Jews (Toor *et al.*, 1957) immigrating to Israel. During the last 2,000 years, these people, wandering in the Arabian deserts or living in Ghetto conditions in Arabian towns, have by segregation remained a relatively "pure" race. Some have immigrated to Israel recently and others have been there for twenty years: the Israeli medical service is common to both. The relevant heart disease mortality rates in 1953–55 for the recent immigrants are 490 per million, compared with 3,300 per million for those who have been in Israel for twenty years (Table II). This makes an interesting comparison with England and Wales, where the relevant rates were 490 deaths per million in 1931 and 3,590 in 1957.

TABLE II.—CORONARY HEART DISEASE: ENVIRONMENTAL VARIATION (Toor *et al.*, 1957)
Mortality Rates Per Million. Arteriosclerotic and Degenerative Heart Disease. Yemenite Jews Immigrating to Israel. Men Aged 45–64 years

Recent immigrants	490
Immigrated circa twenty years ago ..	3,300

Possible genetic factors.—By a well-conceived clinical, biochemical and social survey Epstein *et al.* (1957) were able to show a difference in prevalence of coronary heart disease in two groups of people similar in respect of many environmental factors believed to be important—but differing in race. Jews born in the U.S.A. of European Jewish immigrants were compared with Italians born in the U.S.A. of Italian immigrants. They were similar in sex and age; in the same occupation; similar in body-build, the frequency of overweight and in the total fat in their diet as expressed as a percentage of total calories; similar in the presence of factors known to be associated with coronary heart disease—e.g. hypertension, xanthelasma, diabetes mellitus. They had the same prevalence of previously undetected coronary heart disease. These Jews and Italians did differ a little in mean serum cholesterol and in the percentage of animal fat in their diet. However, they differed markedly in the incidence of overt coronary heart disease. The Jews had two to three times as much coronary heart disease as the Italians; and this difference was similar for comparisons of coronary heart disease in various sub-groups, e.g. in the men with low cholesterol, low weight and low blood pressure; in the retired group; and in those dying of an acute "coronary attack" (Table III). The Jewish garment workers also had far more peripheral vascular disease.

This is not conclusive evidence of a genetic factor, of course; but environment seemed to differ little. It might be argued that there was a

TABLE III.—CORONARY HEART DISEASE: POSSIBLE "RACIAL" FACTORS (Epstein *et al.*, 1957)

Italian and Jewish Garment Workers, New York
Males aged 40 years and over
Point Prevalence of Coronary Heart Disease

		Italians	Jews
1	Overt coronary heart disease (C.H.D.)	4%	12%
2	Overt plus previously undetected C.H.D.	7%	16%
3	C.H.D. in men with *low* cholesterol weight, blood pressure	3%	14%
4	C.H.D. in disabled garment workers	30%	44%
5	C.H.D. mortality in retired garment workers (age-adjusted annual death-rate)	8%	22%
6	Death due to acute coronary attack (age-adjusted annual death-rate)	2·7%	4·1%

difference in "temperament" or "drive". If so it was not manifested to any important extent through the "cholesterol pathway" as suggested by Friedman *et al.* (1958). The serum cholesterol level of the Italians and coronary heart disease rates were about the same on average as for white Americans in the Albany and Framingham studies (Doyle *et al.*, 1957; Dawber *et al.*, 1957).

These findings suggest that environmental changes associated with "progress" and "westernization" are associated with a rise in coronary heart disease; that this association is effective even in races relatively immune in their normal environment, e.g. the Japanese; and that some races are more susceptible than others, e.g. Jews. The disease, however, has been found in all races adequately studied, except perhaps the Bantu in South Africa. In U.S. negroes (Hunter, 1946) and East Chinese (Tung *et al.*, 1958), two populations with reported low incidence, the disease was particularly associated with hypertension.

Thus far, disease due only to *complications* of atheroma has been considered. The prevalence of coronary atherosclerosis itself in its various stages had also to be examined, and this can only be studied in post-mortem material.

Atherosclerosis of Coronary Arteries

This has been studied in relation to its historical trend; to physical activity of occupation; to the main cause of death; and in terms of the prevalence of mural atheroma, and lumen occlusion by Morris (1951) and Morris and Crawford (1958, 1960). The data obtained from more than 200 consultant pathologists, each of whom examined 25 consecutive male bodies aged 45 to 70 years in centres throughout Britain during 1954–56 (National Necropsy Survey) have been analysed; and they have also been compared with Professor Turnbull's findings at the London Hospital during 1908–13.

Comparison of hearts from deaths not due to coronary heart disease itself showed an interesting dissociation of coronary atheroma, or mural disease, from coronary lumen occlusion.

(1) *Secular trend.*—Fig. 1 shows that in

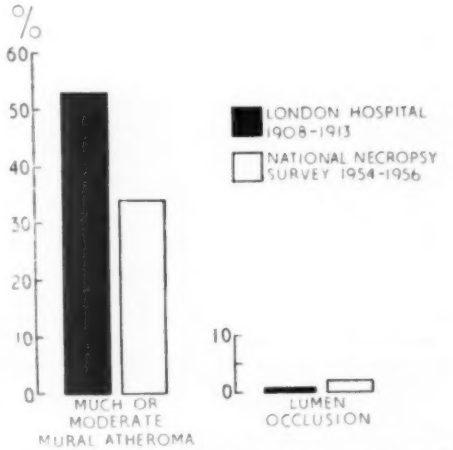

FIG. 1.—Coronary atherosclerosis—mural atheroma and lumen occlusion over half a century. Males, 45–59. Deaths due to cancer, infection, injury. 1,900 cases (Morris and Crawford, 1960).

patients who had died from cancer, injury or infection—the data least likely to be biased for our purpose—the incidence of much or moderate atheroma of the walls of the coronary arteries is if anything less in 1954–56 than in 1908–13: while the incidence of obliteration of the lumen has increased more than twofold. (The same story is told using modern London Hospital material.)

(2) *Physical activity of occupation.*—Independently of knowledge of the pathological findings the occupations of the subjects of the National Necropsy Survey were assessed in terms of physical activity into characteristically light occupations, characteristically heavy, and an intermediate group. Fig. 2 shows that for the 3,800 non-coronary deaths, in men aged 45–70 years, much coronary atheroma (that is "numerous and widespread lesions, all four main

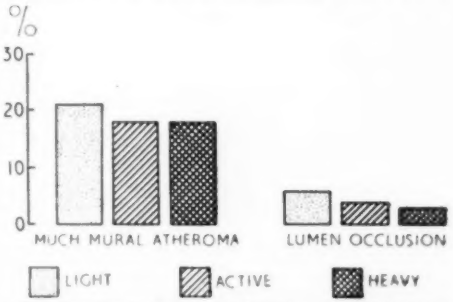

FIG. 2.—Coronary atherosclerosis—mural atheroma and lumen occlusion in relation to physical activity of work. Males, 45–70. All non-coronary deaths. 3,800 cases (Morris and Crawford, 1958).

arteries affected; or more than one extensive area of confluent disease") was about equally prevalent in the three grades of occupation. But coronary occlusion (that is "more than ¾ reduction of the lumen in one or more main artery"; or "pinpoint" stenosis) was twice as prevalent among those in a light occupation as in the heavy work group.

(3) *In relation to main cause of death.*—The 1 400 male subjects aged 45–59 years dying from cancer, injury or infection were compared with 120 subjects who died of peptic, gastric or duodenal ulcer (Morris and Crawford, 1960). Much atheroma was equally prevalent in the ulcer and non-ulcer groups, but coronary occlusion was four times as common in subjects dying of peptic ulcer.

These findings suggest that coronary occlusion has increased in recent years in excess of mural disease, that occlusion is favoured by physically light work, and that something (perhaps diet) associated with peptic ulcer also promotes occlusion. Multiple factors seem to be involved and, although associated, atheroma cannot be equated etiologically with occlusion. The more atheroma is present the more likely is occlusion to be found. But other factors also obviously are important in producing occlusion.

The prevalence of atheroma and occlusion in 2,851 males aged 45–70 years who died from some other cause than coronary heart disease and did not have *hypertension* was compared with 731 subjects also dying of non-coronary causes but in whom there was evidence of essential hypertension. Much atheroma was far more prevalent in the hypertensive subjects and occlusion also was increased. It seems that hypertension favours the development of mural disease and, with this, of occlusion.

Linkage of independent observations.—The post-mortem findings of an increase in coronary occlusion in recent times is in keeping with independent statistical and clinical observations which indicate an increase in coronary heart disease and particularly in acute myocardial infarction. The finding of more occlusion in the light-work group than in the medium and heavy work groups corroborates the independent observation of lower mortality rates from "sudden" coronary deaths in postmen and bus conductors than in socially similar, but more sedentarily employed, post-office clerks and bus drivers.

Clinical-epidemiological survey.—These and other observations prompted a detailed clinical, biochemical, dietary and social study of central London bus drivers and male conductors of double-deck buses. These men were apparently similar in many respects (e.g. there is a difference of only about 5s. per week in wages). The nature of their work differed, however; and it has been known since 1949 that they had a different incidence of coronary heart disease, particularly as "sudden death" in the younger men. It is somewhat premature to report, but it is already clear that the average driver differs from the average conductor, age by age, in respect of height, weight, waist circumference, skinfold thickness, blood pressure under various conditions, plasma cholesterol, beta-lipoprotein and Sf factors (Table IV). In all cases the means are higher for drivers than for conductors, although there are wide individual ranges in both occupations.

TABLE IV.—ANATOMY AND PHYSIOLOGY OF WORKING BUSMEN DRIVERS AND "DOUBLE DECKER" CONDUCTORS, LONDON TRANSPORT

Physique, Casual Blood Pressure, Blood Lipids
MEAN VALUES

Factor		40–49 years	50–59 years	60–64 years
Weight (kg)	Drivers	73·4	74·3	71·6
	Conductors	64·9	67·4	63·3
Height (cm)	Drivers	173	172	171
	Conductors	171	170	166
Skinfold thickness (mm: sum of 3)	Drivers	44	47	52
	Conductors	33	37	34
Casual systolic blood pressure (mm Hg)	Drivers	140	155	162
	Conductors	139	148	156
Casual diastolic pressure (mm Hg)	Drivers	86	90	91
	Conductors	84	86	87
%Blood pressure 160/95 or over	Drivers	10	29	28
	Conductors	4	16	19
Total plasma cholesterol (mg%)	Drivers	249	254	262
	Conductors	228	238	246
Beta-lipoprotein (mg%)	Drivers	202	199	201
	Conductors	169	191	187
Sf 20–400 (mg)	Drivers	161	176	124
	Conductors	107	89	98

Numbers in age—occupation groups ranged from 22 to 184.
Blood lipid analysis by Courtauld Institute of Biochemistry, Middlesex Hospital.

These findings do not yet clarify the issue, as more variables have been introduced; but it is hoped that a study of the interrelationship of these variables may be helpful. Since the range of all the factors mentioned is considerable a follow-up study might prove fruitful.

Diet and cholesterol.—No summary of the epidemiology of atherosclerosis would be complete without reference to diet and blood cholesterol—which are now the main fields of inquiry.

Fat consumption (especially that containing saturated, or short-chain fatty acids—mainly of animal origin) has been associated with blood cholesterol level and to some extent both have been found to rise with economic improvement (although the U.K. evidence is that the rise in

fat available during the present century is mainly due to increase in hydrogenated vegetable fat (Unilever, 1958)).

The Framingham Community Study (Dawber *et al.*, 1957) shows that follow-up of 900 men aged 45–62 years, clinically free from coronary heart disease at the time of admission to the study, gave an overall incidence of new disease of 1·5% per annum. Men characterized by high cholesterol initially had an incidence of 2% per annum. A similar new incidence rate was shown by men characterized by high blood pressure without high cholesterol. Those who had both factors showed a new incidence rate of 4% per annum.

Wilkinson (1958) in family studies found that the incidence of coronary heart disease is more closely associated with hyperlipæmia (triglyceride level) than with hypercholesterolæmia. Also, it is known that cardiac infarction can take place in the presence of relatively low blood cholesterol. Thus Tung *et al.* (1958) found in 38 coronary cases in East Chinese males that the mean serum cholesterol was 186 mg%; Fidanza (1957) found the mean serum cholesterol of 30 Neapolitan workers three weeks after myocardial infarction to be 205 mg%—and there is evidence that the incident itself may cause a rise in blood cholesterol at this stage of the disease. There is need for much more information on these aspects.

The cholesterol level may be affected by many factors. For example, mean cholesterol is low in groups composed of individuals with a low hæmoglobin level (Table V). Thus in Bloor and McPherson's (1917) anæmic patients mean plasma cholesterol levels of 148, 176 and 205 mg% were found with hæmoglobin levels of 7, 7–9 and 9–14 g respectively. In bank men, bus drivers and bus conductors (1957–9), using a similar method of cholesterol estimation, mean levels rose from 229 to 273 mg% as the hæmoglobin levels rose from 13 to over 16 g%. The reason for this association is not yet clear (protein levels, e.g. have not been considered) but it is not unlikely that Yemenite, Bantu, Costa Rican and Puerto Rican blood contains less hæmoglobin than European Jewish, white South African and white North American. The only inference I wish to draw is that it is premature to conclude that the physiological level of plasma cholesterol is 150 mg%.

TABLE V.—HÆMOGLOBIN LEVEL AND PLASMA CHOLESTEROL

Source	Bloor and McPherson (1917)		Bank men 1958–9 Men aged 40–55		Bus conductors 1957–9 Men aged 45–59		Bus drivers 1957–9 Men aged 45–59	
Hb g%	Nos.	Mean cholesterol mg%	Nos.	Mean cholesterol mg%	Nos.	Mean cholesterol mg%	Nos.	Mean cholesterol mg%
– 7	8	148						
7– 9	14	176					1	148
9–13	6	205					—	—
13–14		220	9	229	22	228	7	243
14–16			19	237	39	239	51	254
16 +			15	245	28	242	21	268

Blood cholesterol analysis by Courtauld Institute of Biochemistry.
Hæmoglobin measurements by Dr. J. W. Stewart of Bland-Sutton Institute of Pathology, Middlesex Hospital.

Blood cholesterol or beta-lipoproteins may well be concerned with the atheromatous process in human beings; but the evidence certainly is insufficient to substitute high cholesterolæmia (which can be measured in life) for "much coronary atheroma" (which cannot).

Conclusion

The available data suggest that inherited factors play a role in the development of atheroma. The mode of action is not clear. There is evidence that temperament and tendency to hypertension, hyperlipæmia and hypercholesterolæmia are inherited. Given a suitable environment these factors may develop and play a part in the production of advanced atheroma and particularly in the development of coronary occlusion. In this simplification it is probable that important unknown factors have been left out.

Environmental factors now thought likely to be important are: (*a*) Dietary fat either through hyperlipæmia, or through hypercholesterolæmia, and action on thrombus formation, and on the lysis mechanism. (*b*) Physical activity through dynamics of the coronary circulation, and the formation or lysis of thrombus. (*c*) Mental stress, through temperament, on eating habits—or in some more subtle way. For instance, Friedman *et al.* (1958) suggest that men characterized by "continuous involvement in multiple and diverse functions subject to deadlines" have, particularly at periods of crisis, a raised serum cholesterol and blood-clotting time.

At each stage good evidence is scanty and speculation is rife but, making an "integrated guess", it seems reasonable to focus on the

partial dissociation of coronary atheroma from coronary occlusion as a likely point of break-through in the attempt to halt and turn back the tide of atherosclerotic heart disease in developed countries, and to prevent its occurrence in developing countries.

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Methods of Observing Thrombosis *in vitro*

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THE Greek word *θρόμβος* means a lump, piece or clot in the most general sense. However, it is necessary to make a distinction between a clot which develops *in vitro* and a thrombus that forms *in vivo* because microscopically these two structures are quite different.

Fig. 1 shows the elaborate structure, with areas of pale amorphous material fringed by leucocytes and interspersed with areas of red cells, that is found in a typical thrombus from a patient who died of pulmonary embolism. The pale amorphous material is derived from agglutinated platelets, but this is not obvious from the appearance of the section although it has generally been assumed to be the case and confirmatory evidence is given below. In short, a thrombus consists of masses of agglutinated platelets, the platelet masses being fringed by leucocytes, and arranged in a sort of loose coralline structure, the interstices of which are filled with red cells and, as can be shown by appropriate staining methods, fibrin.

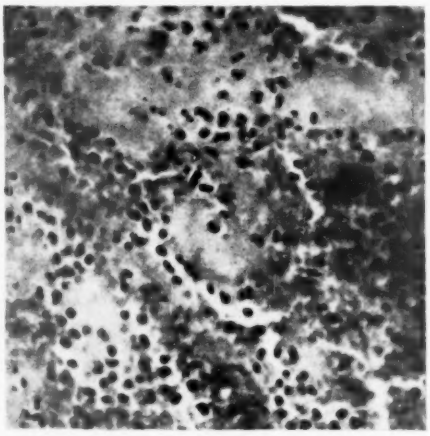

FIG. 1.—The "white head" of a natural thrombus. H. and E. × 360.

Fig. 2 shows a blood clot with an entirely different appearance. All the blood cells, including the platelets, are distributed at random and none is agglutinated. In a more highly magnified field (Fig. 3) a platelet can be seen with various processes coming out of it, but it is a single platelet and not part of a clump.

Thus a clot and a thrombus are very different. In fact the structure of a thrombus may be even more complicated, and frequently two quite well demarcated regions can be made out known as the "white head" and the "red tail". The "white head" has the composition already described of platelet and leucocyte masses, whereas the "red tail" is composed mainly of red cells and fibrin. The "red tail" in fact forms an extension of the red cell and fibrin regions in the "white head" which fill the interstices between the platelet and leucocyte masses, and has a structure not unlike but not quite the same as that of a clot.

Because of these structural differences it is

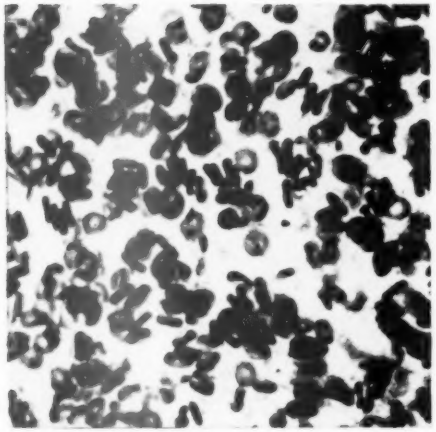

FIG. 2.—Blood clot. H. and E. × 640.

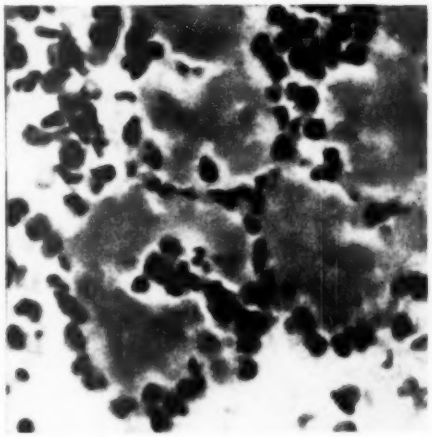

FIG. 4.—The "white head" of an artificial thrombus. H. and E. × 640.

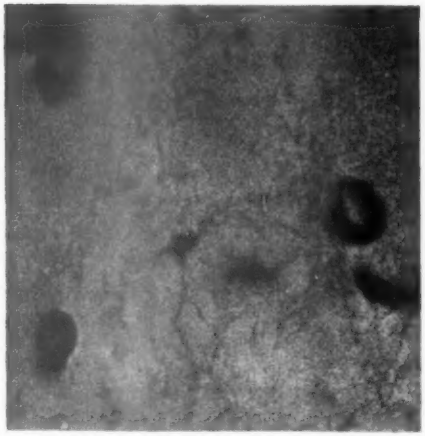

FIG. 3.—Blood clot. H. and E. × 1,500.

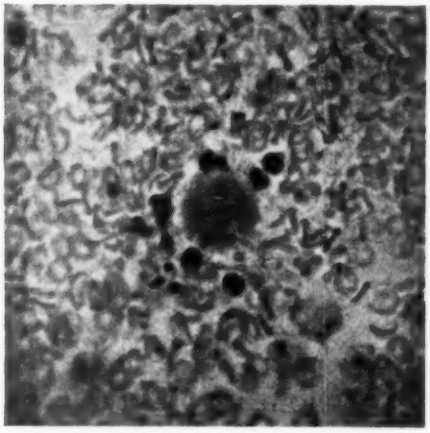

FIG. 5.—Primary clump of platelets and leucocytes embedded in blood clot. Hæmatoxylin. × 640.

obvious on purely morphological grounds that there can be no guarantee that factors affecting the size and speed of growth of thrombi will be accurately revealed by studies of blood clotting. Consequently there is a great need for experimental techniques to bridge the gap in our knowledge between these phenomena.

In the past various techniques have been used. Shionoya (1927) and Best *et al.* (1938) produced arteriovenous shunts in experimental animals, and showed that a structure with the histological appearances of a thrombus was formed. Mason and Harrison (1949) poured heparinized blood down a long glass tube with a side-arm plugged with absorbent material soaked in tissue extract. Again, something not unlike a thrombus was formed.

Chandler (1958) made an important advance when he mounted a closed circular loop of plastic tubing partially filled with blood on a rotating turntable, so that the blood flowed round the loop. When the blood solidified part of it had a histological structure closely resembling a thrombus. Chandler's work has been confirmed in the present study and if the ends of the tubing are joined together so as to produce

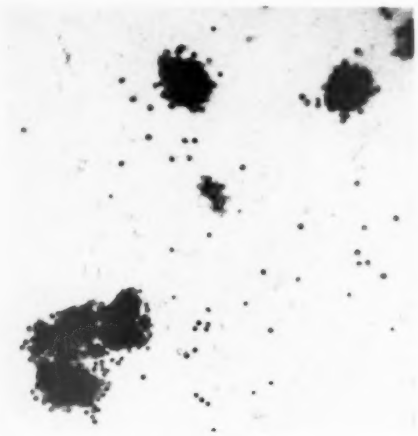

FIG. 6.—Clumps of platelets and leucocytes in a film preparation. Leishman's stain. × 110.

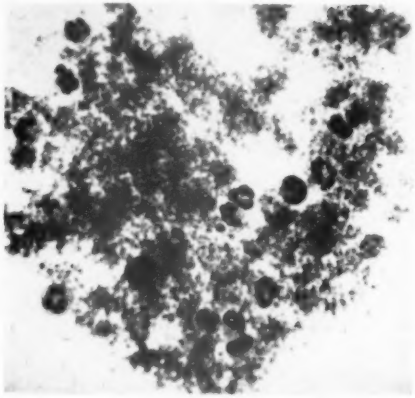

FIG. 8.—Squash preparation of clump of platelets and leucocytes. Leishman's stain. × 460.

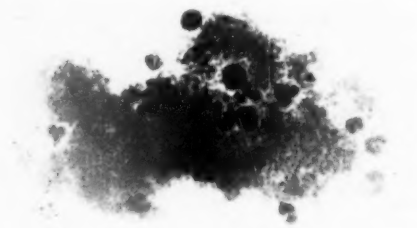

FIG. 7.—Single clump of platelets and leucocytes. Leishman's stain. × 390.

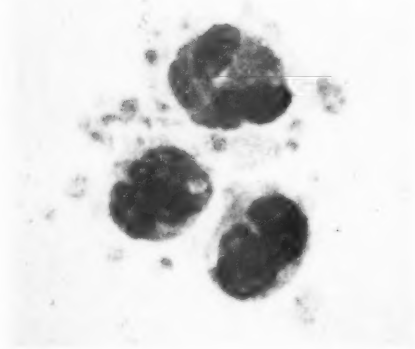

FIG. 9.—Cellular clump consisting of platelets, two monocytes and an eosinophil. Leishman's stain. × 1,500.

a really smooth junction, the structure formed resembles a natural thrombus even more closely. Under these circumstances the blood does not clot at all, in the sense that it never completely solidifies. Instead, a small solid body forms just behind the advancing edge of the column of blood and this floats round with the blood for an indefinite period. Microscopically it is composed of two parts which correspond closely to the "white head" and "red tail" of a natural thrombus. The "white head" is composed of agglutinated platelets, or material derived from platelets, surrounded by leucocytes, and the "red tail" is made up mainly of red cells and fibrin. Fig. 4, a section through the "white head" of one of these artificial thrombi, shows masses of platelet material surrounded by leucocytes and red cells in the interstices of the structure.

Because something very like a natural thrombus is formed by this technique, the sequence of events leading up to the formation of these artificial thrombi has been studied. If, after about one minute, the blood that has flowed round the tube is poured into a glass test tube, it clots quite rapidly and sections cut through this clot show single clumps of the amorphous platelet material with a covering of leucocytes (Fig. 5). These primary clumps then stick together in small groups as can be seen at a slightly later stage. Still later all such clumps unite to form a single loosely-packed structure which is the "white head" of the artificial

thrombus. No further change takes place for several minutes and then, quite suddenly, the "red tail" of fibrin and red cells appears. This is fully formed in a matter of seconds and no obvious further change takes place.

There is another method of studying the initial stages in the formation of these artificial thrombi which has certain advantages. Since no detectable difference was found when freshly drawn blood or recalcified citrated blood was used, it was a natural step to discover what happened with cell-rich plasma obtained by allowing citrated blood to sediment: i.e. plasma from which the red cells had been removed but containing all the other formed elements of the blood. With such cell-rich plasma a "white head" is formed which looks just like the "white head" formed when whole blood is used and the main difference is that instead of a red tail made up of fibrin and red cells there is a tail formed of fibrin only.

With cell-rich plasma, the initial stages in the formation of the artificial thrombus can be studied in another way. Instead of pouring the material from the loop of plastic tubing into a glass test-tube and letting it clot as a solid lump, it can be poured over a glass slide and allowed to clot as a thin film which is then stained like a blood film. Fig. 6 is a low-power view of such a preparation. Two of the primary clumps are seen plus a structure which appears to have been formed by three of these clumps sticking together. At a higher magnification (Fig. 7) it is obvious that these clumps are made up of platelets and leucocytes. Evidently something in the process of fixing and embedding the specimens for histological examination breaks up the platelets into a structureless mass as in Figs. 4 and 5. By gently squashing such clumps, preparations can be made in which the cellular composition can be observed easily (Fig. 8).

By looking at a large number of squashed clumps and fragments of squashed clumps (Fig. 9) it has been possible to establish that platelets, monocytes and granulocytes of all three kinds are incorporated in these clumps, whereas lymphocytes and red cells are not.

Thus, the stages in the formation of these artificial thrombi appear to be as follows. First, platelets, polymorphs and monocytes stick together to form small round clumps with the platelets inside and the leucocytes on the surface. Second, these clumps coalesce to form a single loosely-packed structure which we may provisionally call the "white head" of the artificial thrombus. Third, after an interval, fibrin forms round the "white head", in its interstices and streaming out behind it; if red cells are present, many of them are trapped in the fibrin network forming a "red tail". Two events in this sequence can be timed with reasonable precision. One is the first appearance of platelet and leucocyte clumps. The other is the first appearance of fibrin. A point which may be of some significance in understanding the mechanism of thrombosis is that the times at which these two events—cellular clumping and fibrin formation—occur, can be varied independently. By adding heparin to the blood or plasma in increasing concentrations, the formation of fibrin is delayed and may be suppressed altogether. But even with concentrations of heparin as high as 3 units per ml, the cellular clumps appear at the normal time and go on to form a "white head" of normal appearance. Similar results were obtained with a coagulation defect produced *in vivo*—the prothrombin deficiency which can be induced in animals by feeding excess vitamin A (Harris and Moore, 1928; Light *et al.*, 1944; Walker *et al.*, 1947; Poole, 1958). Again cellular agglutination was not delayed but fibrin formation was.

This is a promising experimental system which may help us to explore the borderland between clotting and thrombosis, because the observations made with blood *in vitro* produce objects the microscopical structure of which closely resembles that of a thrombus *in vivo*.

Acknowledgments.—Much of the experimental material described in this communication was demonstrated at a meeting of the Pathological Society of Great Britain and Ireland held in Oxford in January 1959. A fuller account has been published in the *Quarterly Journal of Experimental Physiology*. The Editors of the *Quarterly Journal of Experimental Physiology* have kindly given permission for the reproduction of the photomicrographs which appear here as Figs. 2, 4 and 5.

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SECTION II

Chairman—J. St.C. Elkington, M.D.

Atypical Angina

By Raymond Daley, M.D., F.R.C.P.

London

It is difficult to distinguish between typical and atypical angina pectoris, as so few patients have the classical constricting sensation in the chest on effort. In 1768 Heberden described angina in a paper entitled "Some account of a disorder of the breast" and it is remarkable that it was not until 1912 that Herrick of the Mayo Clinic associated coronary artery occlusion with the pathological background of angina.

Afferent pain fibres arise in sympathetic nerves which run along the coronary arteries. They pass to the spinal cord via the first to the fourth, and sometimes the fifth, dorsal sympathetic ganglia. The parasympathetic nerve supply to the heart is by the vagi, which have synaptic connexions in the ganglia of the cardiac plexus, or in the intrinsic cardiac ganglia. Inhibitor and constrictor fibres are said to predominate in the vagal, and dilator and accelerator fibres in the sympathetic nerves. The cause of cardiac pain appears to be a disproportion between the inflow of the proper quantity of coronary blood of adequate quality, and the work of the heart.

It is not known whether oxygen deficiency in the coronary venous system directly stimulates pain-sensitive afferent nerve endings, or whether it alters myocardial metabolism and leads to nerve stimulation by excessive or abnormal metabolites. Relative anoxia is essential in the production of pain but it must be realized that the metabolic effect of myocardial ischæmia is slight or absent if the oxygen supply and demand are proportionately reduced, as in hypothermia.

Coronary venous blood is normally, of course, much undersaturated with oxygen. When arterial blood is undersaturated or chronic anæmia is present the myocardium continues to extract oxygen in normal amount so that the undersaturation of coronary venous blood may be intense. Under either of these circumstances angina is far from universal which lends support to the suggestion of metabolite nerve stimulation. It is a matter of passing interest that a good stimulus to the production of intercoronary anastomoses in experimental animals is chronic anæmia but this is not observed in cyanotic congenital heart disease. This does not mean that a state of chronic anæmia is desirable in anginal patients but it may be part of the explanation why many patients with pernicious anæmia lose their pain when the anæmia is corrected.

Injection studies with a lead agar mass have shown that every patient over the age of 60 with symptoms of angina pectoris has occlusion of at least two coronary vessels of at least 60μ diameter.

The problem of coronary spasm remains unsolved. The evidence produced in favour of its occurrence is the occasional attack of angina at rest unaccompanied by tachycardia; sudden death without evidence of major coronary arterial occlusion; and as an explanation for the mechanism of action of small doses of nitroglycerin which relieve pain without altering cardiac output or blood pressure. The evidence against the occurrence of spasm is that tachycardia is far from universal even when coronary occlusion is known to have occurred; properly authenticated reports of sudden cardiac deaths without arterial disease are very rare, especially if injection studies are made; and, as described below, there is another explanation for the action of nitroglycerin. Coronary flow does vary greatly and is altered by various reflex mechanisms, but whether these changes are associated with primary changes of arterial calibre or due to altered cardiac output or coronary arterial filling pressure is not known. While spasm of any muscular tube in the body may occur, its existence in the coronary vessels is not proven and a little coronary spasm usually implies a coronary occlusion. The impressive fact about "pseudo angina" is that it is usually followed by coronary infarction.

The weight of evidence is, therefore, that anginal pain is likely to occur when one or more

coronary arteries are occluded or when coronary blood flow is drastically reduced in relation to the degree of cardiac work. Each myofibril is supplied by a single capillary and when hypertrophy develops there is no increase in the number of capillaries. Hence it is likely that hypertrophied myofibrils can easily become ischæmic and work at a mechanical disadvantage.

One of the most striking examples of reduced coronary blood flow and left ventricular hypertrophy is aortic stenosis. Here systole is prolonged and there is less time for diastolic coronary arterial filling. The situation is reflected in the electrocardiogram which not only demonstrates left ventricular hypertrophy but also left ventricular ischæmia. When mechanically successful aortic valvotomy is performed in middle life persistent cardiac failure often follows and myofibrils, which for years have been inadequately perfused, remain fibrotic with poor contractile power.

If these concepts are correct it is possibly a little surprising that angina is not always typical, at least when there is left ventricular ischæmia. Why this is not so is not understood. When histories are not typical most objective diagnostic help is obtainable from the electrocardiogram. If this is normal at rest, as it usually is, the patient should be exercised with a physician watching until either pain occurs or he stops for other reasons and the electrocardiogram promptly repeated and scrutinized for ST segment variation. "Trials" of nitroglycerin are usually useless and it must be realized that this drug may relieve other sensations as well as true angina; in particular it will relieve the chest "tightness" of cardiac asthma.

Many attempts have been made to correlate particular patterns of pain with cardiac ischæmia in different areas but there is no proper relationship. I share, with others, the impression that posterior infarction is more likely to be associated with œsophageal symptoms and pain in the right arm rather than constricting girdle pain with radiation to the left arm.

Some examples of unusual site of pain or of unusual spread are worth discussing. Sometimes there is centripetal spread of pain from the arms to the chest. Angina is very rarely felt in the thumbs, a point sometimes of value when trying to differentiate from the history the true angina of effort syndrome from "infectious" angina caught from a business associate. True pain radiating to both arms is most unlikely to be due to anything other than cardiac ischæmia. It is not a feature of other causes of mediastinal pain nor is it of cervical spondylosis. Pain caused by pericarditis is characteristically felt only in the chest and from the onset is aggravated by breathing. Sometimes pain is only felt in the lower jaw, or just between the scapulæ. Only rarely is pain felt in the epigastrium. Increased cardiac work after meals may cause angina and the pain be confused with that of peptic ulceration but the onset is usually immediate rather than delayed for an hour or so. A patient recently told me that he has pain in the forearms in the mornings, which is relieved by defæcation. So-called second-wind angina is sometimes seen in golfers, when they experience difficulty at the second hole but can ultimately complete a round. At times there may literally be first-wind, rather than second-wind, and patients do not experience pain or constriction but belching on effort. I do not know why belching is associated with ischæmia but in another context I have observed at fluoroscopy a patient develop paroxysmal tachycardia and angina, and there was no doubt that following the onset of the paroxysm he began to air-swallow.

Angina tends to be aggravated not only on effort but also under any circumstances where there are vasoconstrictor influences, and an increasing number of patients complain of pain when watching boxing or crime plays on the television. Laughter, of course, produces vasodilatation, and the effort of laughter very rarely causes pain. Some years ago I had a patient who developed angina at rest every Sunday morning, and when his reading matter was changed from one paper to another he was spared his angina!

Anginal pain of any type will be aggravated by pain elsewhere in the body. If in addition the source of the pain, such as in gall-bladder or œsophageal disease, has the same paths of nervous reference there is yet a further reason for aggravation of angina. Investigators have inflated balloons in the bile-ducts and lower end of the œsophagus, and observed a reflex reduction in coronary blood flow. Operations on either of these organs usually produce only temporary relief and anginal pain returns as there are further coronary occlusions. I personally have never encountered angina associated with a "knuckle" hiatus hernia in a young person and I think that when such a person has symptoms which mimic angina there is coronary artery disease already present and pain is due to a temporary reflex reduction in coronary blood flow.

There is much discussion about the surgical relief of anginal pain. Unfortunately there is not yet available an operation which will adequately perfuse an ischæmic myocardium. It is well known that any operation which involves opening the pericardium will partially or com-

pletely remove severe anginal pain. Unfortunately operations directed towards the relief of angina have been based on the assumption that new blood vessels can be directed into the myocardium and there has never been post-mortem proof of this. It is much more likely that any interference with the epicardial surface, whether it be a hæmopericardium or the instillation of an abrasive substance or even the presence of pus, will destroy afferent sympathetic nerve endings and hence reduce pain by a "direct" sympathectomy. Following any of these events the patient is usually much more happy and is left with only very atypical angina. If his previous angina has been due to left ventricular ischæmia it will probably be replaced by dyspnœa on effort which will halt him at the same distance at which his angina previously occurred. The electrocardiogram will have ST segment displacement as before operation. If he is not halted by dyspnœa an ache under the chin will remind him of his previous angina and this is probably vagally mediated.

Does acute coronary insufficiency exist? I believe that it does, although it is not common. There is usually increasing angina of effort culminating in prolonged attacks of angina at rest. It is difficult to know whether a course of anticoagulants given to such patients, while they are resting, really averts coronary infarction but at least such treatment is rational and often provides a satisfactory improvement in pain.

Angina, of course, more commonly is associated with coronary disease of the left ventricle and interventricular septum, or in any condition in which there is increased left ventricular work. However, there are examples of right ventricular angina associated with pulmonary stenosis or primary pulmonary hypertension. There appears to be no difference in the quality of pain experienced when either ventricle is incriminated. I have not encountered a patient suffering from right auricular angina, but I believe that some patients with giant left auricles have a form of angina. The pain is aggravated by effort and breathing 10% oxygen. It usually radiates to the right arm and is relieved only after fifteen to twenty minutes' rest. It is sometimes helped by nitroglycerin.

Amongst the known actions of nitroglycerin are systemic vasodilatation and tachycardia, both of which will decrease coronary artery blood flow. The benefit obtained from nitroglycerin must, therefore, be due to an extraordinary degree of coronary artery dilatation or to some other metabolic effect. Experimental cardiac infarction in animals is followed by an increased lactate and pyruvate content in coronary sinus blood and the amount can be reduced by giving nitroglycerin.

Paroxysmal tachycardia is sometimes accompanied by angina but I believe this only to be true when there is co-existing coronary artery disease. Angina may also occur with paroxysmal auricular fibrillation but a curious feature of ischæmic heart disease is improvement of pain when auricular fibrillation becomes established.

I once conducted a clinic for patients suffering from angina alone and it became very obvious that the season of the year, the political climate, and the state of my temper had such a profound effect on the frequency and severity of pain that the number of nitroglycerin pills consumed per day appeared to be a poor guide to the assessment of the anatomical severity of coronary artery disease.

Diagnosis of Carotid and Vertebral Artery Stenosis

By John Marshall, F.R.C.P.Ed.

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The diagnosis of partial or complete occlusion of the carotid or vertebro-basilar arteries is no longer an academic exercise. Surgical treatment of carotid occlusions is well established (Rob and Wheeler, 1957), and although the place of anticoagulant therapy in cerebrovascular disease is far from clear, it is in vertebro-basilar ischæmia that there is most evidence to support its use (Millikan *et al.*, 1955).

Carotid Occlusion

The clinical presentation of occlusion of the internal carotid artery is highly variable (Fisher,

1951, 1954). The vessel has been ligated with impunity many times, while, on the other hand, its occlusion may be accompanied by complete infarction of the anterior two-thirds of the cerebral hemisphere. Between these two extremes a wide variety of deficits may occur. From among these, four modes of presentation may be distinguished as a help in the recognition of the condition. The most pathognomonic, but unfortunately not the most common, picture is that of attacks of transient monocular blindness preceding the eventual onset of hemiplegia on the opposite side. These attacks of blindness last only a few minutes and occur at irregular intervals over weeks or even months before the contralateral hemiplegia develops. Sometimes the blindness may persist, again being associated with a contralateral hemiplegia. The second most characteristic mode of presentation is by recurrent transient attacks of hemiparesis, dysphasia or sensory disturbance down one side of the body. There may be no abnormal signs between the attacks or there may be a residual deficit which increases with each attack giving rise to the so-called "stuttering" mode of onset. This mode of onset is highly suggestive, but not diagnostic of a carotid stenosis as the following case report shows.

A man of 45 years had an attack of dysphasia lasting a few hours in January 1957. Two weeks later he had a further attack of dysphasia accompanied by a right facial paresis and hemiparesis lasting about an hour. In July 1957 he had a third attack which left him with a permanent dysphasia and right hemiparesis. A left carotid angiogram carried out two days after the onset of this third attack was normal. His condition continued unchanged until January 17, 1958, when he had a fourth attack. This was marked by an increase in the severity of his residual dysphasia and right hemiparesis, but again it improved over the course of two weeks so that he was able to be discharged from hospital on January 29, 1958. No angiogram was carried out on this occasion. Two days after his discharge from hospital a fifth attack occurred and on this occasion a left carotid angiogram showed an occlusion of the middle cerebral artery with a normal carotid artery. He again improved to some extent, but in January 1959 had a sixth attack from which he has made little recovery.

A third mode of presentation is as a slowly progressive cerebral lesion. This may appear in the form of a progressive dementia (Fisher, 1954) or a progressive focal lesion may suggest the presence of cerebral tumour (Clarke and Harris, 1958). The fourth and probably the commonest mode of presentation is as a hemiplegia of sudden onset indistinguishable from the common "stroke" which the textbooks are accustomed to attribute to thrombosis of an intracerebral artery. Sometimes there have been premonitory symptoms such as transient pareses, paræsthesiæ or dysphasia over the preceding days or weeks, but not infrequently, despite careful enquiry, no such history is obtainable, the stroke having developed suddenly in a hitherto healthy person. Accompanying the hemiplegia there is usually sensory loss and not infrequently a hemianopia.

Physical examination may contribute to the diagnosis of a carotid occlusion. Palpation of the internal carotid artery in the neck is of doubtful value, but as it is so simple a test it should never be omitted. Absence of pulsation is highly significant especially in the acute stage. The presence of pulsation is, however, of no diagnostic value for it is impossible to be certain that it is not the external carotid artery that is being felt. Probably more information can be gained from palpating the vessel in the pharynx, but this is a difficult technique and only yields information with experience. There may also be a bruit over the course of the artery, hence its presence should always be sought (Fisher, 1957; Rob, 1959). Ophthalmodynamometry has also been reported to be helpful in diagnosis (Wood and Toole, 1957). Increasing pressure is applied to the eyeball to the point at which, in patients able to co-operate, vision is lost, or in other patients, occlusion of the retinal arteries is observed with the ophthalmoscope. In cases of carotid stenosis the end-point pressure is significantly lower on the affected as compared with the opposite side. The technique is not easy, and an observer requires considerable experience before he can rely upon the result. Another sign of diagnostic value is the development of a Horner's syndrome on the affected side (O'Doherty and Green, 1958). This may be slight in degree, but if present, and especially if seen to develop during the period of observation, is of great value.

It will be seen from this clinical account that the certain recognition of cases of carotid stenosis by clinical means alone is not always possible, hence the place of arteriography has to be considered. Arteriography is a very effective way of demonstrating a carotid stenosis. The problems are: (1) It is not without hazard. Exacerbation of symptoms and signs does sometimes occur following arteriography though as yet there are no reliable figures available as to the frequency of this occurrence in a series of patients with cerebrovascular accidents. (2) While we know that a carotid stenosis may present as an ordinary stroke, we do not know what percentage of ordinary strokes are due to carotid stenosis. For example, in a series of 50 acute cerebrovascular accidents investigated by

angiography 6 were found to be due to carotid stenosis, partial or complete, and in only one of these did the clinical story lead us to expect that in fact a carotid stenosis would be present. Without knowledge of these two factors, viz. the incidence of carotid occlusions as a cause of strokes and the frequency of arteriographic complications, it is not possible to state whether arteriography should be carried out or not. We are at Queen Square making a systematic study of the problem by investigating arteriographically all the strokes admitted to our care. As yet the series is insufficient to enable us to make a dogmatic statement. At present therefore it would seem reasonable for the physician faced with this problem to reserve arteriography for the highly suggestive cases such as those with transient monocular blindness or recurrent episodes, or for young patients in whom the possibility of other lesions mimicking a cerebrovascular accident is of greater importance. In the ordinary stroke in the elderly person it would not seem desirable that arteriography should be, or indeed need be, routinely carried out.

Vertebro-basilar Stenosis

The recognition of carotid stenosis and the development of surgical treatment tended to obscure our awareness of the fact that the blood supply to the brain is dependent upon the integral action of four arteries, viz. the two carotid and the two vertebral arteries. Moreover carotid stenosis is most commonly due to atherosclerosis, a condition which affects not one but many arteries simultaneously. The importance of maintaining a holistic view of the problems of cerebrovascular disease was emphasized by the work of Hutchinson and Yates (1956, 1957) who found, when the great vessels of the neck were examined in a series of 83 autopsies, that 10 had significant carotid stenosis, 7 significant vertebral stenosis but 23 had significant stenosis of both vertebral and carotid arteries.

There appear to be two main ways in which vertebro-basilar stenosis may present, one being as a sudden, rapidly fatal illness, the other as progressive or recurrent episodes of cerebral disturbance. It is with the latter we are mostly concerned as offering some possibility for therapeutic intervention.

The presenting symptoms are those of a disturbance of brain-stem function. Not infrequently there have been premonitory symptoms such as vertigo, dysarthria, confusion and transient limb pareses over the preceding weeks or months. Temporary dimness of vision due to impairment of the blood supply through the posterior cerebral arteries may also have occurred. The definitive illness is usually marked by paresis of one or both sides of the body often accompanied by sensory loss. If the upper brain-stem is mainly involved, diplopia, abnormalities of eye movements, pupillary disturbances and nystagmus are present. If the lower brain-stem is involved, facial palsy, dysarthria and dysphagia may be prominent along with vertigo. One striking picture is that of disturbance of consciousness without much in the way of focal cranial nerve involvement. Thus a picture very like that of akinetic mutism may be seen without there being much else to indicate that the lesion is in the brain-stem.

A decision about angiography is easier to make in the case of vertebral stenosis than it is for carotid stenosis. The technique is more difficult; there is a strong clinical impression that the incidence of complications in cases of cerebrovascular disease is not inconsiderable; and there is at present no surgical treatment of proven value for vertebral stenosis. For these reasons it would not seem advisable to attempt to confirm the diagnosis by arteriography. Moreover the clinical picture is more distinctive than in many cases of carotid stenosis. Hence those who wish to use anticoagulant therapy can reasonably do so on the basis of the clinical diagnosis alone.

The recent increase of interest in cerebrovascular disease has emphasized the great lack of knowledge which exists about many aspects of the condition including the diagnostic. With so common a condition it should be possible to establish clinical diagnostic criteria and to verify their validity by post-mortem examination with relative ease and rapidity. This urgently requires to be undertaken if we are to reap the full benefit of advances in therapeutics.

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Atherosclerosis of the Arteries of the Limbs

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ATHEROSCLEROSIS is a disease of large vessels and rarely affects the small vessels. Collateral arteries are immune, as are the smaller main vessels such as, in the lower limbs, the dorsalis pedis artery, the plantar arch and the digital arteries. Though the collateral vessels themselves are not affected, in long-standing cases and particularly when gangrene threatens, their origins may be "nipped" as they pass through the diseased walls of the larger arteries from which they arise. This is an important factor in the final failure of the distal circulation.

The fact remains that when obstruction is proximal the distal arterial tree is filled with blood through collateral vessels and the digits of the limb whose arteries are patent receive a supply usually adequate for the part at rest. Generally therefore there is no gangrene unless the crises of injury or sepsis occur and cannot be met by the increase of blood flow demanded in such circumstances. It must be remembered that a finger the site of a whitlow requires a blood flow almost twenty times that of a normal finger, and if this cannot be achieved, then necrosis or gangrene may follow. Gangrene may also follow embolism of distal vessels by a thrombus dislodged from a proximal plaque of atherosclerosis or an extension of thrombosis started by an incident of hypotension complicating an operation or severe illness—the so-called post-operative gangrene.

Because the distal arteries remain patent, any procedure which will overcome the proximal obstruction will relieve symptoms and the hazards associated with an ischæmic limb. Although atherosclerosis is a generalized and progressive disease it often remains static for long periods. A patient may suffer intermittent claudication from femoral obstruction without increase of severity for many years and without disease elsewhere, e.g. in the coronary or cerebral arteries. In fact symptoms may lessen because not only does the collateral circulation increase with time but also the patient learns to avoid the use of the claudicating muscles. However, arterial obstruction in atherosclerosis at one site must be taken as an indication of diseased arteries elsewhere. It appears that aorto-iliac disease is more commonly complicated by coronary or cerebral arterial accidents than is femoral, but even so such complications may be long delayed. Therefore, if it is possible by direct arterial surgery to relieve the proximal obstruction, this is a proper procedure to be considered when the disability is significant.

Regarding the arteries of the lower limbs, disease of the aorta must be considered. There is a distinct pattern of disease in these vessels, though atheroma itself does not cause symptoms unless narrowing is extreme or obstruction complete from superadded thrombosis. Lindbom (1950) demonstrated the incidence of atheroma in his experience and most will agree with his findings. The commonest site of intimal thickening and subsequent obstruction is the superficial femoral artery at or about the adductor hiatus. Furthermore the whole of this artery up to the level of the bifurcation of the common femoral artery and down to the upper part of the popliteal artery is similarly, though less, prone to disease. Following close behind the superficial femoral artery in its susceptibility to disease come the common iliac arteries which are frequently affected bilaterally and involve the terminal aorta.

There is also a common pattern of disease in the lower leg. The posterior tibial and, to a lesser extent, the anterior tibial arteries are often obstructed, sometimes in patches, sometimes in the whole of their course, though there is a distinct tendency for their terminal parts to remain patent, the vessels of the forefoot rarely being affected by atherosclerosis. The peroneal artery, like the profunda femoris in the thigh, usually escapes disease. Dible (1956) has shown that the arrangement of collateral vessels in the leg resembles in function, if not appearance, the arterial arcades seen in the branches of the superior mesenteric artery. As some of the main branches of this artery can be obstructed without critical diminution of blood supply to the intestine, so both tibial arteries can be obstructed and the patent distal arterial bed will still be supplied through the peroneal. Therefore if a pulsatile flow under good pressure can be restored to the distal popliteal artery and so to the peroneal artery recovery of the severely ischæmic foot, even one bearing frankly gangrenous toes, often results, though the dead digits will subsequently be cast off.

From a consideration of this pathological anatomy, certain clinical features can be better understood and a more accurate prognosis of the future of the diseased limb can be made.

Intermittent claudication is the commonest symptom, but though most common in the calf

muscles it may also occur in the foot, thigh or buttocks, according to the site of arterial obstruction, and sometimes must be distinguished from foot strain and sciatica. It occurs in the upper part of the limb when obstruction is in the aorta or iliac arteries. In general, trophic changes in the extremities are less the higher the obstruction in the arterial tree, though wasting of calf muscles may be prominent. Colour changes are important, though with the limb at rest and horizontal they are often absent. Rubor on dependency is a sign of severe and long-standing ischæmia but if replaced by pallor on elevation indicates patency of the distal arterial tree. Persistence of rubor or cyanosis irrespective of posture indicates obstruction of the distal vessels by embolism or secondary thrombosis often initiated by trauma or sepsis and in these circumstances gangrene is imminent. Rest pain varies with ischæmia. It increases with the severity of the ischæmia and decreases with improvement of blood supply. Rest pain is in fact an excellent gauge of the efficacy of treatment. It is a sinister symptom and unless it can be relieved gangrene will occur within three to six months.

With regard to sepsis and ulcers in the ischæmic limb, the nature of the discharge indicates very readily the chances of healing in a particular case. If the disease is frankly purulent—if in fact the pus is "laudable"—then the blood supply is adequate because production of such pus is part of the process of repair. If, however, the discharge is watery, then healing is improbable.

As to the indications for sympathectomy in atherosclerosis, sympathectomy will increase the blood flow in the distal part of the limb and will usually double the resting flow. Exercise demands a seven- to ten-fold increase, and therefore sympathectomy cannot be expected to have any effect on intermittent claudication. Nor has it. In the presence of trophic change in the toes sympathectomy is a useful measure if for some reason a graft cannot be done. When rest pain is present a careful assessment must be made, as failure of sympathectomy to relieve this symptom is a serious matter.

We use the following test to determine the effects of the operation for rest pain. The patient is confined to bed and encouraged to exercise his leg freely. Sympathetic release is encouraged by vasodilators, alcohol, reflex heating of the trunk and the use of barbiturates to achieve deep sleep. If after a week of this regime pain is eased, then a sympathectomy is advised. If it is not, then amputation is recommended.

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Renal Artery Stenosis

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ATHEROMATOUS disease within the renal artery has lately aroused considerable interest not primarily because of its effect upon renal function, which may be slight except when thrombosis occurs, but because the ischæmic kidney may cause hypertension similar to that produced in experimental animals by the Goldblatt clamp (Goldblatt, 1937). Apart from the theoretical interest of this lesion as a cause of hypertension it is of considerable practical interest in that surgical treatment of the renal artery disease may produce reversal of the changes of apparently progressive malignant hypertension.

Atheroma of the renal artery may occur without other obvious manifestations of arterial disease or it may be associated with other atheromatous lesions and it was the investigation by aortography of patients with aortic and iliac disease that drew attention to the renal changes and the possibility of surgical treatment.

In 1956 Professor Rob and I operated upon a patient aged 39, who presented with symptoms of aortic thrombosis—severe buttock claudication and inability to maintain an erection. He had a blood pressure of 205/110—and an aortogram (Fig. 1) revealed thrombosis of the aorta from the level of the renal arteries downwards, with stenosis of the left renal artery. At operation both renal arteries were stenosed. Aortic reconstruction was performed and an attempt made to perform a thrombo-endarterectomy on both renal arteries. This was successful on the right side but was not possible on the left and the left kidney was removed. The patient's claudication was relieved and he is now, three years after operation, normotensive.

Such cases raised the possibility of occult renal arterial lesions being a cause of hypertension. A number of cases have now been described in which surgical treatment of such a lesion has produced apparent cure of progressive hyper-

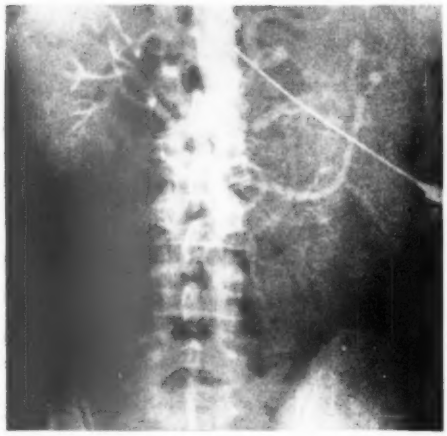

FIG. 1.—Aortogram showing aortic thrombosis from the renal artery level downwards with stenosis of left renal artery.

tension, the biggest series being those of Poutasse (1956) and DeCamp and Birchall (1958).

At St. Mary's Hospital Professor W. S. Peart has become interested in this problem and the investigation of hypertensive patients for such a lesion has led to the discovery of a number of cases. There are as yet no adequate figures from which to assess the incidence of renal arterial disease in the ætiology of hypertension but, whatever the incidence, it is worthy of consideration with other potentially curable causes of hypertension such as phæochromocytoma.

Diagnosis

(1) *Clinical.*—There is often nothing in the clinical history which differs from the usual history of a hypertensive patient but there may be an absence of a family history, the patient's age may be outside the usual range for malignant hypertension, or there may be a history of pain in the loin suggesting renal infarction.

On physical examination there is one sign which is suggestive of the disease—the finding of a systolic murmur over the renal artery on abdominal auscultation.

(2) *Intravenous pyelogram.*—A slight difference in size or function between the two kidneys may need a much more critical evaluation than in assessing the usual renal causes of hypertension. An interesting finding in one of our patients was a consistently increased pyelographic shadow on the affected side, probably due to normal tubular function in the presence of impaired glomerular filtration.

(3) *Divided renal function studies.*—Mueller *et al.* (1951) demonstrated that the first alteration in renal function produced by experimental ischæmia is a depression of the urinary sodium concentration. This forms the basis of the Howard test (Howard *et al.*, 1956) in which renal function tests are performed simultaneously on ureteric catheter specimens. In the present series water excretion, sodium and chloride concentration and creatinine and PAH determinations have been done. The most significant finding has been depression of the sodium and water excretion on the affected side. A number of practical difficulties were encountered in the performance of this test, the greatest being the collection of complete specimens from each side without a leak to the bladder around the catheters. Levinsky and Berliner (1959) suggested that alteration of urine composition does occur in the bladder so that a calculation based on the assumption that the bladder urine is unchanged renal urine may not be valid.

The success of these studies has been due to the great patience of Dr. J. I. D. Robertson.

(4) *Arteriography.*—This is essential to the diagnosis. These investigations have been performed by Dr. David Sutton and the lesions have been demonstrated by percutaneous aortography or by selective catheterization of the renal arteries through a femoral artery. The lesion usually occurs in the proximal part of the artery, close to the aorta (Fig. 2), and may be associated with post-stenotic dilatation. The kidney may be demonstrably smaller and areas of infarction seen.

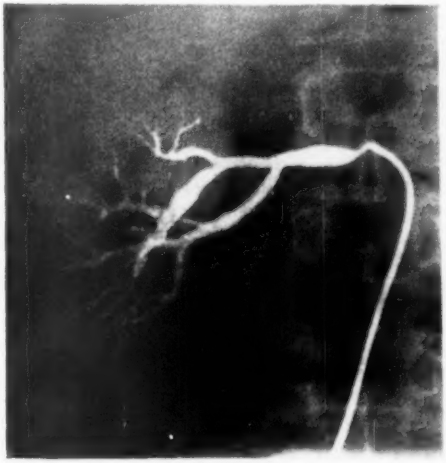

FIG. 2.—Renal arteriogram showing stenosis of the right renal artery near its origin.

Although the radiological appearances are extremely valuable they should not be regarded as diagnostic of a functional stenosis without other supporting evidence, including the demonstration at operation of a lowered arterial pressure or blood flow distal to the stenosis. In several cases radiological defects in the artery have been unassociated with any demonstrable ischæmia, and in one case it was evident that the interference of flow produced on arterial catheterization had resulted in artefactual stenosis.

(5) *Renal biopsy.*—In most cases renal biopsy has been only of retrospective value, the biopsies being taken as part of the definitive operative treatment. Pre-operative percutaneous biopsy would seem theoretically valuable but in the pertinent cases biopsy was particularly difficult because of a very small kidney or an aberrant blood supply.

(6) *Arterial pressure measurements.*—As soon as the renal artery and aorta are exposed at operation simultaneous pressure recordings using a capacitance manometer are made with needles in the two vessels. In cases of true stenosis an appreciable pressure gradient has been demonstrated, a difference which disappears or is markedly reduced after surgical treatment.

Treatment

The simplest surgical treatment is nephrectomy, which may be indicated in patients of poor general condition or following a failed conservative operation. It has been advocated when the kidney is grossly atrophic on the side of the stenosis but there is as yet no evidence as to the degree of atrophy which is irreversible.

In most patients it seems desirable to perform a reconstructive arterial operation and restore normal bilateral renal function. The kidney on the affected side may be potentially better than the opposite kidney as it is protected from secondary hypertensive changes by its stenosis. Various operations have been suggested and it is too early to assess their respective merits fully.

(*a*) *Thrombo-endarterectomy.*—The removal of the plaque from the renal artery together with any thickened aortic intima at the origin of the vessel is a relatively quick and straightforward operation. It may occasionally, however, be difficult to gain access to the origin of the vessel on the right side because of the close relationship of the vena cava and left renal vein.

(*b*) *Renal artery re-implantation.*—The artery may be divided and anastomosed to a fresh site in the aorta. Alternatively, side-to-side anastomosis of the renal artery to the aorta may be performed below the level of the stenosis. When the stenosis is in the middle of the artery it may be excised with end-to-end anastomosis.

(*c*) *By-pass grafting.*—A by-pass graft may be inserted from the aorta to the distal renal artery. An alternative on the left side is to anastomose the splenic artery to the distal renal artery after removing the spleen.

Other more complicated operations have been suggested but it would seem probable that one of the procedures mentioned will give the most satisfactory results.

During the operation the aorta is clamped obliquely so as not to interrupt the blood flow to the opposite kidney.

Results

In 5 cases where the lesion was proved at operation there was no operation mortality or morbidity. A bilateral case is described above. This patient, treated by nephrectomy on one side and thrombo-endarterectomy on the other remains normotensive three and a half years after operation.

Two similar male patients, one aged 48 and the other 50, with severe progressive hypertension and marked retinal changes have been treated by thrombo-endarterectomy. In one of these patients this was followed by thrombosis, necessitating nephrectomy on the affected side. In both patients the blood pressure dropped from pre-operative levels of 230–240/150 to 130/90 and the eye changes regressed, one patient within six months and one nine months following operation.

A female patient aged 48 with a pre-operative blood pressure of 220/120 was treated by nephrectomy, rather than by a conservative operation, as she had a small kidney on the side of the stenosis and lived abroad where follow-up would be difficult. Her blood pressure has become normal three months after operation.

A male patient aged 40 with a pre-operative blood pressure of 210/110 has been treated by side-to-side anastomosis but the operation is too recent for any assessment to be made.

Although the follow-up period in these patients is relatively short it is probable that specific relief of the hypertension has been obtained. The fall in blood pressure is probably not merely the result of a non-specific operation as it occurred slowly during the months following operation.

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SECTION III

Chairman—PAUL WOOD, O.B.E., F.R.C.P.

Blood Coagulation, Thrombosis and Atherosclerosis in Ischæmic Heart Disease

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A CLOSE association between the presence of atherosclerosis and the development of ischæmic heart disease is widely accepted. However, ischæmic heart disease may develop in the presence of remarkably little atherosclerosis of the coronary arteries, and gross coronary atherosclerosis may be present in individuals who never develop myocardial ischæmia. Other ætiological factors in ischæmic heart disease must be sought, and it has been supposed that increased coagulability of the blood may be one. Recently we have explored this possibility.

Investigation of Blood Coagulation in Ischæmic Heart Disease

Blood coagulation was first compared in 48 patients with ischæmic heart disease and in 48 normal subjects of the same age and sex (McDonald, 1957; McDonald and Edgill, 1957). All the patients had angina pectoris on exertion; although cardiac infarction had occurred previously in some of the cases, it was recent in none. The age and sex distribution were typical of ischæmic heart disease. The ages were from 40 to 62 years, average 53, and there were 42 men and 6 women.

Tests of blood coagulation, performed on patients and controls under uniform conditions, covered the various phases of blood coagulation: thromboplastin-generation test, platelet count and estimation of platelet stickiness, fibrinogen estimation, two different prothrombin times (using Russell's-viper venom, Stypven, and brain extract, Thrombokinase, Geigy), three different contact-clotting times (using ground glass, Ballotini spheres, and a silicone tube), and estimation of factor VII in plasma and serum.

Comparison of the mean values for patients and normals showed significant differences in relation to thromboplastin generation (Fig. 1), platelet stickiness (Fig. 2), fibrinogen estimation and prothrombin time (Russell's-viper venom, Stypven). These results indicated increased coagulability of the blood in the patients with ischæmic heart disease, compared to the normals of the same age and sex. The differences were significant at the 1% level, except the prothrombin time (Russell's-viper venom, Stypven) where it was at the 5% level. A statistically significant difference was not found between patients and controls in total platelet counts, contact-clotting times, estimation of factor VII in plasma and serum, or in the prothrombin times using brain extract (Thrombokinase, Geigy). Thus for the first time, hypercoagulability of the blood in ischæmic heart disease was clearly demonstrated. Subsequently these differences were found to remain unaltered on repeated testing. In a joint examination of platelet

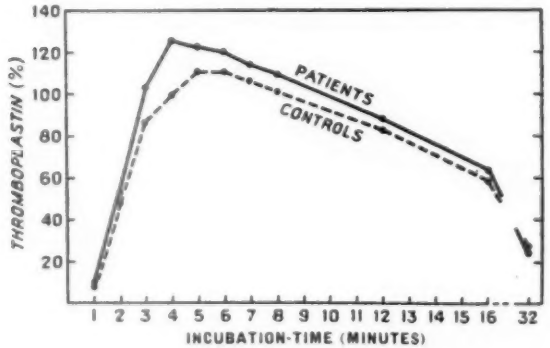

FIG. 1.

FIG. 1.—Thromboplastin-generation test: averages for patients and controls (8·5 sec = 100%).

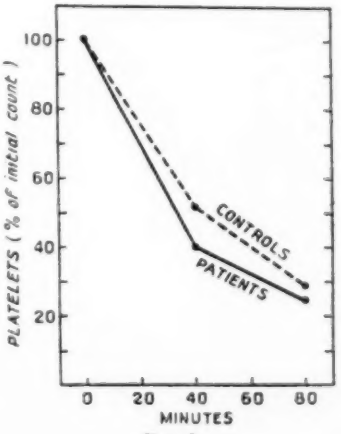

FIG. 2.

FIG. 2.—Platelet-stickiness test: averages for patients and controls. The remaining percentage of the initial platelet count reflects the stickiness of the platelets.

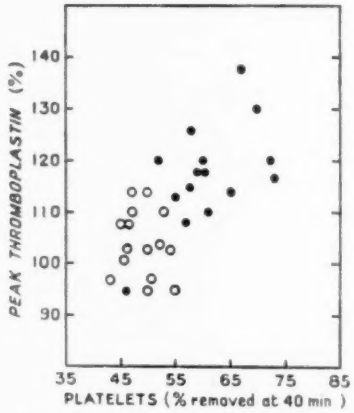

FIG. 3.—Relation between peak percentage reached in thromboplastin-generation test and platelet-stickiness (recorded here as % of initial platelet-count removed at 40 min, i.e. 100 minus % remaining): solid circles, patients; open circles, controls. Figs. 1–3 are reproduced from McDonald and Edgill (1957) by kind permission of the Editor of the *Lancet*.

stickiness and thromboplastin generation, in 15 paired male patients and controls, a definite relation between the two tests was established for the patients but not the controls (Fig. 3).

Blood coagulation (i.e. thromboplastin generation, platelet stickiness, fibrinogen estimation, and prothrombin time using Stypven) was next compared in normal subjects and in patients with angina pectoris on exertion, acute coronary insufficiency, and recent cardiac infarction (McDonald and Edgill, 1959). Mean values for platelet stickiness, fibrinogen estimation and thromboplastin generation significantly increased from normal subjects to patients with angina pectoris, and from these to patients with cardiac infarction (Fig. 4). The differences were significant at the 1% level, except that between the mean values for patients with angina pectoris and cardiac infarction which was nearly significant at the 5% level. Findings in acute coronary insufficiency were not significantly different from those in angina pectoris, except that the platelet count was significantly higher, at the 5% level, in acute coronary insufficiency (*see* Table I) than in normal subjects and patients with angina pectoris. This finding remains unexplained.

TABLE I.—PLATELET COUNTS IN NORMAL SUBJECTS AND IN PATIENTS WITH ANGINA PECTORIS, ACUTE CORONARY INSUFFICIENCY, AND CARDIAC INFARCTION

	No. of subjects	Mean of platelet counts per c.mm whole blood, in thousands*	Standard error	Pooled standard deviation within group
Normal subjects ..	22	256·0	10·7	
Angina pectoris ..	30	245·7	9·2	
Acute coronary insufficiency	7	314·4	19·0	50·2
Cardiac infarction	10	280·5	15·9	

*For significance of differences *see* text.

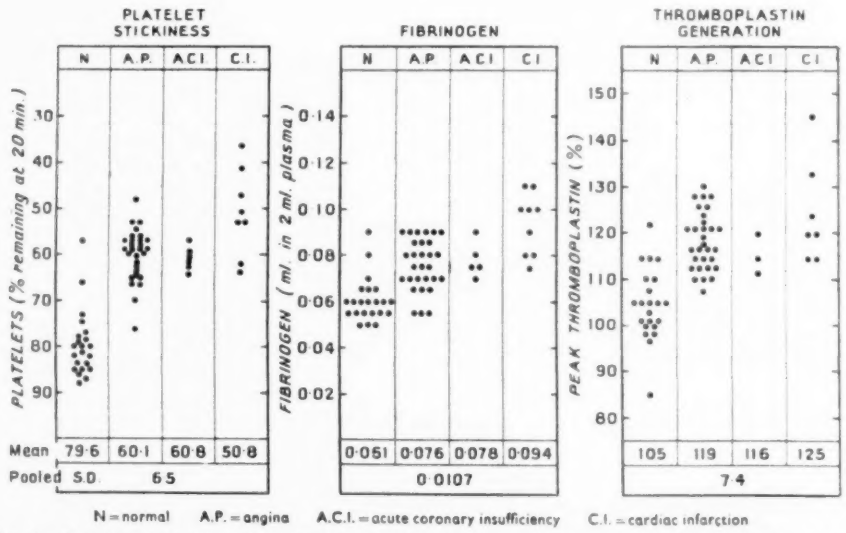

FIG. 4.—Blood coagulability with regard to platelet stickiness, fibrinogen estimation, and thromboplastin generation, in normals, and in patients with angina pectoris, acute coronary insufficiency and cardiac infarction. Reproduced from McDonald and Edgill (1959) by kind permission of the Editor of the *Lancet*.

The mean platelet count in patients with cardiac infarction was intermediate, and did not differ significantly from the others. On repeated testing platelet counts varied more in patients with ischæmic heart disease than in normal subjects; this may be related to the increase found in acute coronary insufficiency.

These studies therefore confirmed the hypercoagulability of the blood that we had described previously in patients with angina pectoris, and showed that hypercoagulability was greater after cardiac infarction. The facts are in full accord with the clinical observation that patients with ischæmic heart disease have an increased tendency to thrombosis.

Discussion

The significance of hypercoagulability.—Tests of blood coagulation which are performed *in vitro* must be considered in relation to coagulability and thrombosis *in vivo*. They may be assumed to reflect coagulability of the blood *in vivo*, and thrombosis is likely to be associated with hypercoagulability. It would, of course, be preferable to study thrombosis within the patient, and impaired fibrinolysis and thrombolysis may yet prove to be of paramount importance. Absolute figures in any of the tests of blood coagulation may permit only limited interpretation; the comparison of normal subjects with patients, or of patients in different phases of their disease, is more valuable. Increased platelet stickiness may merely reflect the presence of intravascular thrombosis (Bobek and Cepelak, 1958), and we have found it increased in extracardiac thrombotic conditions.

An important question was whether hypercoagulability is a cause or an effect of ischæmic heart disease. Relative hypercoagulability of the blood exists in some normal people, but there is no evidence as yet that this predisposes to ischæmic heart disease. Hypercoagulability may well be an effect of ischæmic heart disease rather than a cause. This is not to deny that temporary hypercoagulability, followed by thrombosis, might not initiate the disease, nor that previous hypercoagulability might not increase with it.

There are at least three possible reasons for hypercoagulability after recent cardiac infarction. A phase of hypercoagulability may immediately precede infarction, initiate coronary thrombosis, and persist after the acute episode. On the other hand, hypercoagulability may merely reflect the presence of recent thrombosis, or be caused by tissue damage and intravascular stasis. The natural history of ischæmic heart disease could be affected by hypercoagulability of the blood in different ways. Thus an increased tendency to mural thrombosis, leading to atherosclerosis (Duguid, 1946), and a greater likelihood of complete arterial occlusion by thrombosis, would be expected if hypercoagulability is associated with an increased tendency to thrombosis.

Anticoagulants.—Various anticoagulants act differently in restoring hypercoagulability of the blood towards normal. Thus heparin rapidly depresses thromboplastin generation to normal levels and below, and platelet stickiness is reduced towards normal, although the effect is less. Phenindione affects both these tests less. The possibility of heparin deficiency or overutilization is being further investigated. In anticoagulant therapy with phenindione, the optimum amount of the drug is usually judged by the prothrombin time. However, the amount of anticoagulant needed probably varies with the degree of hypercoagulability. It is not surprising that some patients develop thrombosis despite adequate treatment by phenindione as judged by the prothrombin time. Ideal anticoagulant therapy might be based on the titration of the right anticoagulant against clotting factors which are known to be abnormal.

With regard to anticoagulant therapy in the management of ischæmic heart disease, it seems reasonable to assume that any measure which safely corrects hypercoagulability and returns blood coagulation to normal should improve the prognosis.

Action of fats.—It has been thought likely that the activity of platelets in blood coagulation is due to ethanolamine phosphatide or some related compound (O'Brien, 1956); but at present "not enough is known about the connexion between clotting and thrombosis to decide whether or not the part played by fats in blood coagulability is relevant to the mechanism of thrombosis" (Poole, 1958). Modification of the diet may, however, produce an anticoagulant effect. Diminished platelet stickiness and lowered serum cholesterol have been found after the rice-fruit diet (McDonald and Edgill, 1958), but there was no evidence that the change in stickiness was due to the reduction of cholesterol, as opposed to some other metabolic change. When serum-cholesterol was lowered by corn oil in hypercholesterolæmic patients, coagulability of the blood remained unaltered (McDonald, Edgill and Murdoch, unpublished).

Conclusion

There is clear evidence of phasic hypercoagulability when the blood of patients with ischæmic heart disease is studied *in vitro*. This is entirely in keeping with a variable hyperthrombotic state, and ischæmic heart disease is marked clinically by episodes of thrombosis.

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Surgical Treatment of Atherosclerosis

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IRRESPECTIVE of where the lesion lies the surgeon can treat a patient with arterial insufficiency in only one or more of the following ways: arterial reconstruction designed to restore normal or nearly normal blood flow; an operation to increase the efficiency of the collateral circulation; an operation to reduce symptoms by limiting the function of ischæmic tissues; and an amputation or excision of ischæmic tissues. Some patients with atherosclerosis develop arterial aneurysms and here the treatment is surgical whenever the location and clinical findings warrant it and the patient's general condition permits it.

Arterial Thrombosis and Stenosis Due to Atherosclerosis

Until recently surgeons have concentrated on the management of patients after an artery has thrombosed (Rob, 1953, 1956). Whilst our main efforts are likely to remain in this field I believe that gradually the emphasis will change. The results of surgery in the prethrombotic stage of arterial stenosis are much better and I think that in five years surgeons will be concentrating on what is in some cases a curative operation and in some a prophylactic one—the removal of arterial stenoses caused by atherosclerosis.

The reconstructive surgery of stenoses of the carotid and vertebral arteries (Eastcott *et al.*, 1954; Rob and Wheeler, 1957), of the renal arteries (Freeman *et al.*, 1954; DeCamp and Birchall, 1958) and of the aortic arch syndrome (Warren and Triedman, 1957) is now an established procedure. The reconstructive surgery of stenosis of the superior mesenteric artery (Glotzer and Shaw, 1959) and of the coronary arteries (Cannon *et al.*, 1959) is emerging from the experimental stage and, as our skill and knowledge increase, may also become established. In the abdominal aorta and the arteries of the limbs many surgeons have already removed arterial stenoses, as opposed to complete thromboses, with excellent results (Rob, 1957).

The procedures of choice for removing arterial stenoses are thrombo-endarterectomy and direct suture. With these techniques arterial substitutes such as vein grafts, arterial transplants and plastic prostheses are rarely required—a great advantage because follow-up studies show much better results when an artery is reconstructed without the use of arterial substitutes. In my own series the thrombosis rate has been only 18 out of 167 thrombo-endarterectomies (10·8%) and 2 out of 37 direct sutures (5·4%); but when an arterial substitute has been used the incidence of thrombosis has risen to 90 out of 401 operations or 22·4%. These figures are for a follow-up of between one month and nine years, the average duration being more than two years.

The diagnosis of arterial stenosis as opposed to thrombosis.—The clinical effects of these two lesions may be identical, particularly in the case of the internal carotid artery. But more patients consult their doctor after a complete thrombosis has occurred because for obvious reasons the symptoms are usually more severe. It is of importance that a patient with a complete thrombosis of one artery may have a stenosis of one or more other arteries. It is from these patients that one can learn the diagnostic features of arterial stenosis as opposed to thrombosis.

Both lesions produce ischæmic effects distal to the occlusion. The distal pulses are usually absent with a thrombosis and present, but reduced in volume, with a stenosis; but when the collateral circulation is particularly good they may be present with a complete occlusion. With exercise these pulses disappear in the latter two types. An oscillometer reveals similar findings. In our experience a particularly valuable physical sign is *arterial auscultation:* about half of the severe arterial stenoses which I have seen exhibited a systolic murmur on auscultation over the site of the stenosis. This murmur is different from the more diffuse murmur, also heard in part of diastole, which appears occasionally over a complete occlusion when the collateral circulation is particularly good. This systolic murmur over an arterial stenosis not only serves to diagnose the lesion but to locate it. For example, in many patients with stenosis of the renal arteries and hypertension it is possible to

decide by this means alone that a renal artery is stenosed and that the stenosis is on the right or left side. Auscultation with the stethoscope pressed firmly on to the abdominal wall about 2 in. (5 cm) above and 2 in. (5 cm) to the right or the left of the umbilicus reveals this murmur. On the strength of this finding we have operated on a number of cases without arteriography and found the expected stenosis.

Arteriography is a valuable diagnostic aid but when the findings on auscultation and by other clinical methods are clear it may be omitted. It is, however, essential in many patients and gives a clear picture of the location of the stenosis; it does not, however, give a clear picture of the degree of stenosis. The stenosis may appear to be slight on the arteriogram but at operation may prove extreme, and, less commonly, it may appear to be severe arteriographically when in fact it is minimal. One reason is that arteriograms are still taken in only one plane, a two-plane view being more useful to assess the constriction produced by a stenosing lesion.

Arterial Thrombosis and Stenosis in Certain Special Vessels

The femoral and popliteal arteries.—We believe that the main indications for reconstructing these arteries is gangrene or rest pain and in limbs which would otherwise be amputated, about 25% can be saved. Another important indication is intermittent claudication of sufficient severity to interfere with the patient's work. But these indications only apply to thrombosed arteries. When a localized stenosis is present it is wise to operate even when the symptoms are mild.

Thrombo-endarterectomy is the procedure of choice for localized lesions of these vessels and sometimes good results follow when long lengths are reconstructed in this way using the semi-closed technique of Cannon *et al.* (1958). But for these long occlusions we prefer a by-pass procedure using a prosthesis of woven Teflon or Terylene or a homologous arterial transplant preserved by freezing. The by-pass should always extend from the common femoral artery to the distal part of the popliteal and we use a synchronous combined technique with two surgeons (Owen and Rob, 1956).

The abdominal aorta and iliac arteries.—Occlusions of these large vessels are best treated by the operation of thrombo-endarterectomy and the results have been satisfactory. But when the occlusion has reached the level of the left renal artery it is usually better to perform a thrombo-endarterectomy of the proximal 3 cm. An arterial substitute is then anastomosed to the end of this stump and to the sides of the distal patent vessels, usually the iliac arteries. On follow-up of 106 of these patients, the combined hospital and later mortality has been 17 (16%), 12 thrombosed this or another artery later and the remaining 77 or 72·6% are alive and well. The follow-up has been for a minimum period of one year and a maximum of seven years.

The internal carotid and vertebral arteries.—These vessels illustrate well the good results which may follow operations for arterial stenosis. The procedure of choice is a thrombo-endarterectomy. This subject was recently discussed at a meeting of the Section of Neurology (Rob, 1959) and will not be discussed again here.

The renal arteries.—Stenosis of these vessels has been discussed by Mr. Owen. As his clinical material closely approximates my own I will consider only one point, the problem of which operation to perform—nephrectomy or the more conservative procedure of renal arterial reconstruction. As he has stated, the factors to consider are the state of the other kidney, the amount of change which has occurred on the diseased side as shown by frozen section histology and biochemistry, and the blood pressure drop across the stenosis. My own opinion is that if the other kidney is satisfactory the preferred procedure is arterial reconstruction; when a doubt exists the right thing to do is to restore a normal lumen to the stenosed vessel. If this is satisfactory as shown by the removal of the pressure drop across the stenosis then all is well; if the pressure drop remains then I think that it is wise to do a nephrectomy at once before closing the wound.

The superior mesenteric artery.—The clinical features of stenosis or slow thrombosis of this vessel were described by Klein in 1921, but it was not until 1958 that Shaw and Maynard first successfully treated this lesion by arterial reconstruction. Now that the clinical picture of chronic mid-gut ischæmia is becoming better known (Mavor and Michie, 1958) it is probable that more of these lesions will be diagnosed with the result that the surgery of this artery will become a well-recognized procedure.

The aortic arch syndrome.—This abnormality which is usually due to an atherosclerotic stenosis of the innominate, carotid and subclavian arteries, together with the dome of the aortic arch, was noted by Broadbent in 1875. More recently Takayusu (1908) and Martorell and Favre (1954) have described this syndrome using the term "pulseless disease". The surgical treatment, which usually consists of a thrombo-

endarterectomy, has been described by several surgeons including Warren and Friedman (1957).

Stenosis of the coronary arteries.—For years surgeons have been trying to solve the very difficult problem of the restoration of a normal flow through these arteries. Occasional cases have been reported but recently Cannon *et al.* (1959) published their results in 9 patients with thrombo-endarterectomy. It seems that at last the surgical treatment of this lesion may be emerging from the experimental stage.

Other surgical procedures for arterial stenosis and thrombosis.—The natural tendency toward developing a good collateral circulation may be enhanced by *sympathetic ganglionectomy* which is the most effective method of producing a maximum persistent vasodilatation and is a worth-while procedure in many patients. Of the operations designed to limit the function of ischæmic tissues, that of achillis tenotomy (Boyd *et al.*, 1949) has a strictly limited but useful place in the management of intermittent claudication of the calf muscles. Amputations when necessary should be performed without delay but arterial reconstruction procedures have made these less common; in selected patients the transmetatarsal operation is of special value.

Arterial Aneurysms Due to Atherosclerosis

The most common cause of arterial aneurysms is atherosclerosis and in the absence of effective medical treatment most of them should be treated surgically. In most situations surgical treatment by ligature and by-pass or resection and reconstruction is well established and we have performed more than 200 such operations. But the treatment of two lesions still requires further development: these are aneurysms of the proximal part of the aortic arch and ascending aorta, and dissecting aneurysms.

Aneurysms of the proximal aortic arch which involve the innominate artery carry a very high operative mortality. Treatment consists to-day of anastomosing a temporary branched shunt to the sides of the ascending aorta and the necessary distal vessels. But when the ascending aorta has to be resected as well the mortality rises still higher. It is possible that deep hypothermia, 5° C, coupled with complete cardiac arrest, may provide the answer to this problem (Kenyon *et al.*, 1959).

Dissecting aneurysms used to be treated medically and as there were no effective medical measures the results were very poor; to-day some of these patients may be treated surgically. The lesions may be localized or diffuse. The former present few problems, resection and reconstruction with an arterial substitute being the best treatment. The diffuse form can only be saved if there is still evidence of renal function, and if anuria has not developed an emergency operation is indicated. The most satisfactory procedure which we usually employ is to clamp partially both the dissection and the true lumen near to the distal limit of the dissection; we then make a large re-entry foramen from the dissection back into the true lumen. After this the blood in the dissection clots; occasionally a double-barrelled aorta remains. The results of this procedure have been satisfactory. We now believe that all dissecting aneurysms which have not caused anuria should be treated as surgical emergencies.

Summary

(1) The surgery of atherosclerosis has been briefly reviewed.

(2) The concept has been put forward that surgeons will soon be treating many more stenosed, as opposed to thrombosed, arteries.

(3) The value of arterial auscultation in the diagnosis of arterial stenosis has been stressed.

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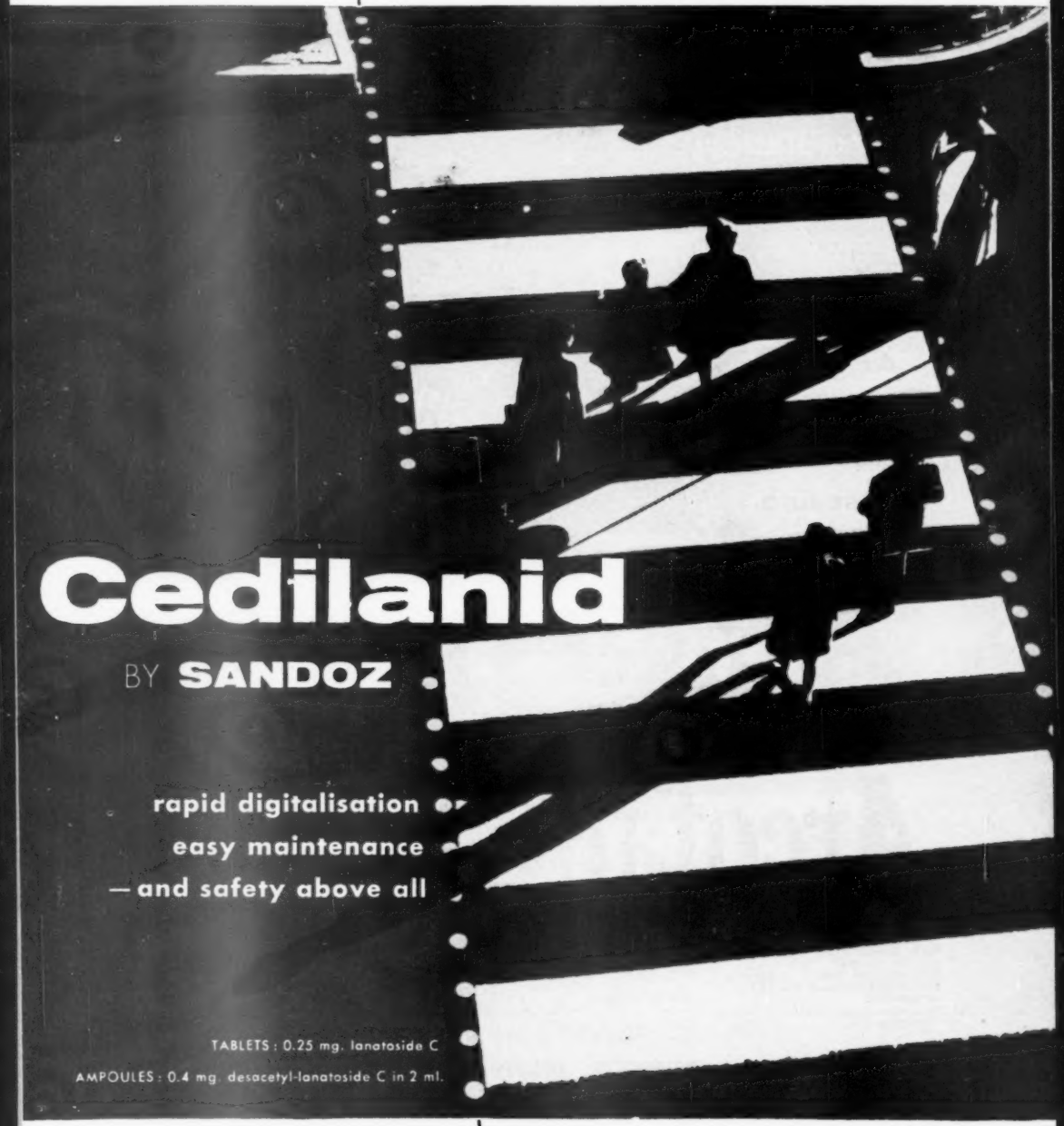

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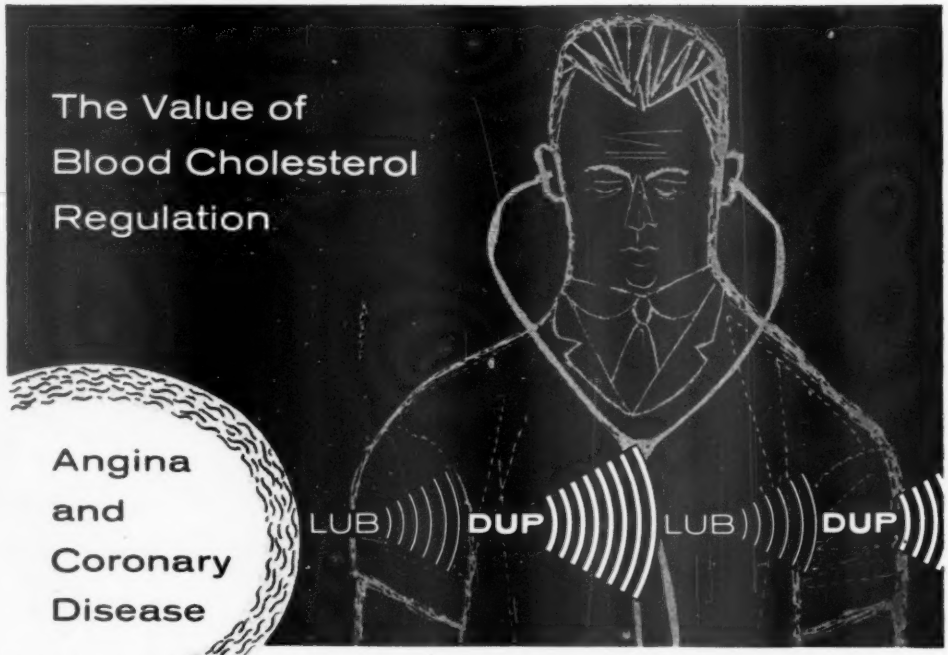

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President—ALAN H. HUNT, M.Ch.

Meeting
November 11, 1959

Wound Healing

PRESIDENT'S ADDRESS

By ALAN H. HUNT, M.Ch.

London

WOUND healing is a commonplace phenomenon, and like all commonplaces in medicine requires to be critically reviewed from time to time. Biologically it is as intricate and insoluble as the problem of growth itself, yet we stitch up the abdomen by a method that has for each of us become a habit, and leave the rest to nature.

In what way can we minimize the chance of a mishap and encourage nature? Can we be satisfied with our present methods? How can they be improved upon? Is it possible or practicable to incorporate modern scientific ideas and technical advances in our day-to-day methods? It is with these thoughts in mind that I chose the subject of wound healing as my Presidential Address because healing looms large in the minds of surgeons dealing with advanced malignant and inflammatory lesions of the colon and rectum.

My interest in the subject has encouraged me to search for basic knowledge which might be helpful, but I have been surprised to find that we can apply in practice little of the great mass of scientific information that has accrued. A quotation from Dunphy (1958) bears this out: "Biochemical and histochemical studies of connective tissue repair have provided a new perspective on the reparative process, but practical application of this knowledge awaits further study." Yet much of the experimental work is beautiful and fascinating and I hope that we shall have opportunities during the coming Session of examining some of the experiments being carried out by Professor D. Slome and Dr. G. H. Blair at the Royal College of Surgeons.

Wound healing has been divided into three phases: traumatic inflammation including the period of cleaning up by phagocytosis, the lag period and then the collagen phase. Yet it is all one vital process which begins at the moment the wound is inflicted.

The Phase of Traumatic Inflammation

The great men of surgery, Halsted, Moynihan and Whipple to mention but three, have all stressed what we now widely recognize—that incisions and dissections should be made with the creation of as little dead tissue and with the use of as little ligature material as possible, leaving the least amount of material to be removed by phagocytosis. It is easy to recognize that sloughs, foreign bodies, clots and infection delay the orderly progress of healing, but are there any methods in common use that should be critically examined?

The plastic surgeons have taught us how to handle skin wounds—hæmostasis of individual bleeding points and exact full-thickness closure without compression or tension. They have made a precise study of the subject in that part of the body that can be seen by the most exacting of our critics, the patient. The methods practised on the surface, where appearance is all-important, should be applied in principle to the depths, where looks may not matter but where results may mean life or death; for example, whether an anastomosis unites satisfactorily or leaks. For this reason I would like to see the all-layers *continuous* "*hæmostatic*" *suture* go out of use. Much slough may sometimes be seen at anastomoses after its use. More trouble should be taken to secure the bleeding points and to construct the anastomosis layer by layer. Non-absorbable sutures should be interrupted and should not, as a rule, impinge on the innermost mucosal layer.

Diathermy is constantly criticized as a source of dead material. These criticisms are justified only if it is not properly and lightly used—either to divide fascial planes, muscle or vascular adhesions, or to coagulate individual minor bleeding points. To do the minimum of damage and achieve its purpose more rapidly than by clamp and tie, it must be used with precision. The finest toothless forceps are necessary for the coagulation of individual vessels.

Method of Closure of Abdominal Wounds

In making our wounds, we do as little damage as possible so that inflammation and phagocytosis, the cleaning-up processes, do not unnecessarily delay the reconstruction. During the early part of healing the wound edges are held together only by fibrinous adhesion and the sutures we introduce. I was taught to close abdominal incisions layer by layer with linen thread or catgut sutures, but disruption and herniation occurred from time to time so I know that method to be wrong. It does not possess strength in depth. The stitches are liable to cut or tear out from the aponeurosis, especially where fibres are arranged horizontally, as at the paramedian region of the rectus sheath in the epigastrium. A stronger closure will prevent dehiscence.

Disruption

It is generally agreed that mechanical strain on the abdominal wall—from abdominal distension combined with coughing or vomiting, sneezing or hiccuping—is the precipitating factor in most of the disruptions. Sepsis of the abdominal wound and the discharge of digestive ferments contribute towards the danger. Systemic and metabolic disturbances, dietetic deficiencies and endocrine disorders are of importance in that they contribute to the danger in about 1 in 4 of the cases (Lund and Crandon, 1941; Hunt, 1941). We can argue about the frequency of disruption, whether it is 0·5% or 3% and whether the mortality is 15% or 50%, but the point is that it should never occur.

When an abdomen has burst and the intestines are in the bed, it is easy to see that the stitches have given way, but it often happens insidiously in the following way, and only the final separation is dramatic. It begins by a small tongue of omentum wedging itself through the peritoneal closure and continuing to be forced out under pressure from inside the abdomen. The stitches are under tension and give way individually as each has to take the brunt of the strain. The process can be likened to a creeping rip. Often the skin stitches hold out so that the full extent of the disruption is only evident when they have been removed. The actual burst is often preceded by a copious discharge of serous fluid and it is then that it needs to be detected, and dealt with.

We close a burst abdomen by approximating the whole of the abdominal incision with all-embracing non-absorbable sutures, such as stainless steel wire, having done our best to bring the peritoneal layer together. An abdomen sutured thus rarely bursts again, yet the circumstances for closure are less favourable than at the time of the operation. If the general idea is correct for a burst wound, surely it is also correct for the prevention of the disruption? I do not insist that it is essential for every situation or every case. The McBurney incision, for instance, is well and securely closed layer by layer with catgut. Most straightforward operations in well-nourished patients do well when closed whichever method is used. It is the chronically ill patients, the undernourished, those suffering from malignant and metabolic disease, the elderly and the obese that we must consider.

The principles of closure, therefore, that I practise in these cases are as follows:

(1) Accurate and close peritoneal closure so as to prevent creeping extrusion of the omentum, using continuous catgut, and often reinforced by including with it the transversalis fascia or muscle. This first layer is only to contain the abdominal contents. It is not expected to take strain.

(2) Strong approximation of the full thickness of the musculo-aponeurotic layers without tension and without strangulation.

The deep approximating sutures are designed to withstand greater strain than a distended abdomen can ever exert and are of the "far-and-near" type (Babcock, 1934). They must be inserted deep in muscle and fascia, at least 1 cm from the cut edge. Each stitch passes down through all layers to the peritoneal closure, and back out through all layers on the other side. This is the "far" part of the stitch. It is lifted so that the wound edges are brought together and the "near" part is inserted to approximate the most superficial layer of the anterior rectus sheath or the external oblique aponeurosis. The knot is tied without tension on the tissues. Fig. 1 shows these stitches diagrammatically for

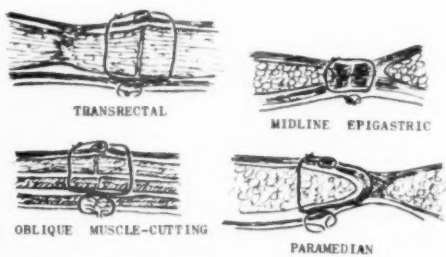

FIG. 1.—Non-absorbable buried ligature used in the closure of four common incisions: transrectal, midline epigastric, muscle-cutting and paramedian. Three are of the "far-and-near" type. Skin and fat are not included.

some of the approaches commonly used. The distance between each should be little more than 1 cm. Often many stitches need to be inserted before they are tied, so that the strain is evenly distributed over the length of the wound and no gaps are left. No one stitch is ever placed to withstand strain individually. It is vitally important that there shall be no space and no tension. The method is one of "apposition in depth".

I claim no originality for the method. Mr. Lawrence Abel proved to me how effective it was, even as a continuous suture, but I have come to the conclusion that interrupted stitches are more sure and less troublesome, though they take longer to put in. Where speed is imperative, a continuous suture is allowable.

The principle of this method is clear, to take the strain by holding the wound opposed rather than by tying it together by the edge. The success of the method depends on the material, particularly when there is any disease or abnormality present that delays healing—malignancy; malnutrition, especially protein and vitamin-C deficiency; jaundice; metabolic or hormonal irregularity; infection or possible discharge of digestive ferments. In each of these circumstances a non-absorbable ligature is essential.

The ideal suture material must be totally inert, so as to stir up no reaction whatsoever on the part of the tissues except fibrosis. It must be fine and of great tensile strength. It must not have interstices that harbour infection and it should, therefore, be a single filament. It must hold on a small knot. Such a material does not exist. *Stainless steel wire* has most of these qualities, but it is stiff and difficult to handle. In time it fragments, even when inserted as interrupted stitches, and then the patient may become aware of its presence and it may cause pricking. But the knot, if tied as a true reef, is small (Fig. 2) and the ends can be cut flush on to it, giving the smallest bulk of any knot. Each end should be cut individually and in full view. My preference is for size 33 standard wire gauge; it rarely needs to be removed. A possible disadvantage of steel is met with in reopening incisions, but the difficulty of finding the stitches can be overcome by using the cutting diathermy instead of the knife. On contact with the wire there will be a small spark showing its position. It can then be caught between hæmostats, divided and removed. Contrary to what has been suggested, it can be ignored in abdominal radiotherapy and short-wave diathermy, and I have yet to have proof that patients closed with wire are more liable to be struck by lightning!

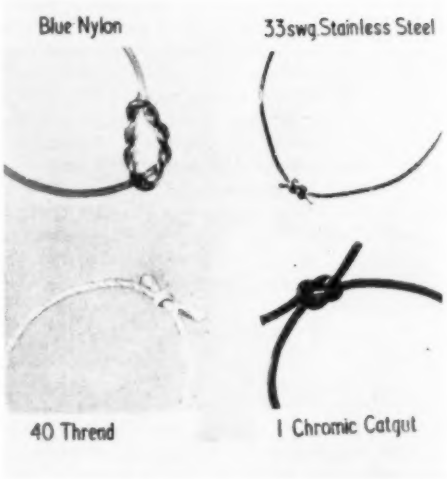

FIG. 2.—Four types of ligature material compared.

Nylon is not so strong (Fig. 2); it causes some tissue reaction and has a slippery surface; it needs a bulky knot and this often gives trouble. In the infected wound it tends to maintain the infection and has to be removed. Someone said in this hall a few years ago, "The great advantage of nylon is that it can be removed so easily when it becomes infected". This inability on the part of nylon (and all other synthetic fibres at present available) to allow infection to grow out past it, is a prohibitive disadvantage. In Fig. 2 the nylon is knotted with a single surgeon's knot, which is the smallest knot that will hold. This could not be pulled up tighter without the filament breaking. Such a knot, far from allowing granulations to grow through it, would certainly harbour an infection.

Steel sutures do occasionally have to be removed for sepsis, especially in the presence of diabetes and other systemic diseases, but less often than nylon.

Cotton or linen thread and silk are the easiest of all materials to use, but they are made up of many filaments and are not suitable for big stitches because they inevitably form sinuses in the presence of infection. These materials, though excellent for hæmostatic ligatures, are of no value for large deep sutures.

The production of the ideal filament is a challenge to the manufacturers of surgical suture materials. It should be as inert as stainless steel, as strong and as supple as thread, a monofilament and rough enough to be tied with a small knot.

It is the knot that is the snag with all synthetic fibres. If it is not possible to roughen the surface sufficiently for a reef knot to hold, would it be possible to invent a means of bonding the stitch in a loop? I have in mind a device in which the ends of the suture could be crossed over in a groove, held, compressed and then heated to fusing point by the momentary passage of an electrical current which would automatically cut out when the correct temperature was reached (Fig. 3). Teflon, I am told, fuses at 200 C, a temperature which could be prevented from harming the tissues in a properly designed instrument. The ends could be cut short on to the bonded segment. I doubt if the whole process would take as long as tying a knot.

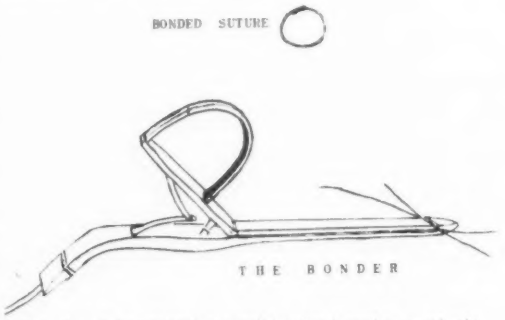

FIG. 3.—A hypothetical machine for bonding synthetic ligatures.

Tension sutures are unnecessary if sufficient strength is incorporated in the depths of the wound. Ugly ladder scars should be a thing of the past (Fig. 4). In this illustration, the initial exploratory paramedian incision has healed less well than the right oblique incision. The former was made as an emergency and in the presence of ascitic fluid, the latter after careful preparation, though with ascitic fluid still present. It is not my purpose in this review to compare the relative merits of different approaches, or where it is best to put the drainage tube. The incision used depends on the disease to be attacked. I desire only to suggest a method of closure which will apply equally well to all abdominal incisions.

Some Biological Aspects of Wound Healing

I have dealt with the points that I consider to be important in choosing the most secure method and material for the closure of abdominal wounds and I have done this with some hesitation in the presence of many surgeons who have been my teachers. In discussing the biological aspects of wound healing, however, I shall be on less treacherous but more difficult ground.

Some aspects of healing are of importance to the biologist but of little interest to the abdominal surgeon, e.g. the source of basement membranes. The migration of epithelial cells concerns specialties other than proctology. Abdominal surgeons are interested most in the proliferation of fibroblasts, their maturation and their capacity to form strong scar tissue by the deposition of collagen. Other matters demand our attention from time to time such as the orderly organization of blood clots, the method of contraction of granulating wounds and the regrowth of muscle. Some matters require urgent study, such as the qualitative and quantitive effect on the healing process of cortisone and like substances.

The Lag Period

Inflammation and phagocytosis begin immediately the wound has been made. Epithelial migration can also be detected at this stage. The proliferation of fibroblasts and their migration into the wound space take some two to five days to become evident. This delay is referred to as the lag or latent period. No one knows what the stimulus to this movement and multiplication is or why it does not begin immediately. If we can shorten the lag period, we shall accelerate

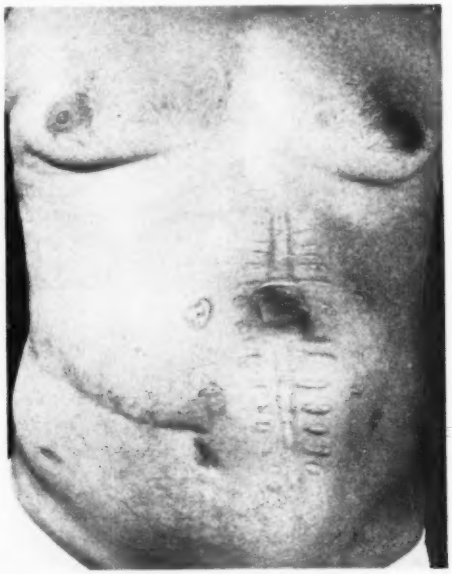

FIG. 4.—Ugly ladder scar compared with muscle-cutting incision closed by the method of apposition in depth.

healing. Dunphy refers to it as the substrate phase, but this is not quite the same thing; the substrate phase is the time during which substances which will be converted into collagen are accumulating in the wound. It undoubtedly begins in the lag period and extends beyond it. Much ingenious work has been done by Dunphy and his associates to discover the substances that accumulate in the wound at this period. They have embedded fragments of sponge within wounds and analysed the fluid that can be collected from them. They have also attempted to overcome the lag period by injecting stimulants into the proposed site of incisions. One such substance is carrageenin, a polysaccharide extracted from Irish moss. The idea is good but a distinction must be made between stimulating the fibroblasts and setting up an inflammation. The only method at present known of eliminating the lag period is to make an incision five days before the definitive part of an operation and to suture it temporarily. The reopened wound will heal more quickly. This is one explanation which in part accounts for the usually satisfactory aftermath in patients who survive a disruption, and for the way in which wounds unite after secondary suture.

Protein in Wound Healing

In 1919 Clark showed that starvation of protein increased the interval before new fibroblasts appeared and also slowed up their multiplication. The lag period is thus increased in protein deficiency and all conditions leading to a reduction of serum proteins, such as inability to absorb protein, excessive utilization of protein in cancer and infections, defective metabolism of protein in liver disease, &c. In many of these conditions there is an inability on the part of the body to replace protein as it is utilized. Clark's observations have been confirmed and expanded in many ways since 1919. For instance, in a normal individual, injury leads to a negative protein balance and an alteration of the following pattern in the circulating proteins:

Albumin decreases from 5·5 to 4·6 g%
Alpha-globulin increases from 1·5 to 2·3 g%
Beta-globulin increases from 1·4 to 1·5 g%
Fibrinogen doubles from 0·4 to 0·8 g%

Feeding with a high-protein diet increases the rate of cellular proliferation, speeds up the healing and reduces the loss of protein.

The sulphhydryl radical has been shown to be the fraction which is of the most significance and its mobilization for the healing of the injured part apparently accounts for the wastage evident in the negative protein balance. Cystine and methionine are the two amino acids in greatest demand. Those parts of the protein molecules not required to supply these two amino acids are thrown out. Methionine alone has little effect. Cystine considerably speeds up cell proliferation and the two together have double the effect of cystine alone.

The growth of fibroblasts occurs, of course, from each side of the wound and ends when both groups of the cells have become linked. The meeting of cell with cell appears to inhibit further growth.

The Collagen Phase

Collagen is a complex protein and constitutes about 30% of all body protein. It and its precursor, precollagen (or procollagen as it is now called), are formed from the substrate substances by the intermediation of ascorbic acid, which is not itself incorporated into the substance of the wound tissue during the healing process. Collagen can be completely dissolved and reconstituted *in vitro*, without the further intervention of the vitamin (Nageotte, 1927). This alone suggests that the vitamin has a function more closely related to the living activity of the fibrocytes than to a chemical reaction in a test tube.

Collagen is made up of 18 amino acids (including proline and hydroxyproline) and other substances that go towards the formation of protein. Mucopolysaccharides (glycoproteins, hexosamine and glucuronic acid) have been isolated from the healing wound by the sponge method and shown to decrease as the collagen content and tensile strength increase. It was the accumulation of these substances that gave rise to the expression "substrate phase".

The amino acids containing the sulphhydryl radical are almost totally lacking in collagen, yet in the body the presence of methionine increases the ratio of collagen to non-collagenous substrate. Here, then, is another substance which enhances the formation of collagen without becoming part of it and yet another reason for feeding first-class animal protein liberally before and after operations and wounds. Methionine, particularly, in the absence of ingested protein, is said to be mobilized from muscle and converted in the liver to cystine. Liver diseases, therefore, are not only associated with a basic deficiency of available proteins but with a defect in the mobilization of suitable amino acids from the protein depots of the body.

Scurvy and Vitamin C

The history of the discovery of the cause of scurvy is one of the most fascinating stories in

medicine. It is linked with the supremacy of the British Navy during the 18th and 19th centuries when it was known by us that fresh fruit juices would prevent the disease (Lind, 1772). Even to this day in some parts of the world the British sailor is referred to as a limey. I therefore make no apology in referring you to a historically significant page from Richard Walter's compilation "A Voyage Round the World by George Anson" (1748), in which he describes how old wounds . . . "in the progress of the disease broke out afresh" . . . and "the callus of a broken bone, which had been completely formed for a long time, was found to be hereby dissolved". Proof has come from work done in many parts of the world (by Aschoff and Koch, 1919, Germany; Wolbach and Howe, 1926; Taffel and Harvey, 1938; and others in America) of the true nature of scurvy. In the absence of vitamin C, collagen, reticulum and the other supporting structures of the body atrophy. If there is damage to the tissues, the supporting structures are not replaced.

Collagen formation is assumed to take place in the extracellular spaces by a chemical process related to the activity of the fibrocytes. Intercellular precipitation generally follows the contours of the mesodermal cells and their fibrils. Doljanski and Roulet (1933) actually demonstrated that collagenous fibrils could form in parts of culture medium free from cells. Recently, however, it has been suggested that the process may after all be intracellular with extrusion of the fibrils into the surrounding medium. Ham and Elliott (1938) were the first to suggest that the process was not strictly one of gelation but possibly a failure on the part of the vital processes of the cells themselves. That all intercellular substances are affected in scurvy also suggests that the mediation of the vitamin entails a common intracellular process because it is unlikely that there would be a common chemical process in the deposition of the different materials. Even in subscurvy the fibroblasts do not mature to fibrocytes (Hunt, 1941) and it is possible that this immaturity in appearance is associated with an incompleteness of function.

Full clinical scurvy is rarely seen. Partial deficiency is not uncommon. Further, wounding or illness causes a state of "physiological scurvy" to develop, the excessive demands on the vitamin causing a delay in the healing of subsequent wounds, which can be rectified by greater supply of the vitamin. It may be taken as generally agreed, therefore, that plenty rather than just enough of the vitamin should be administered for the formation of collagen to take place to best advantage, even though normal health can be sustained in the intact individual on a fraction of the quantity of the vitamin necessary to maintain saturation.

The processes involved can be illustrated experimentally in guinea-pigs, comparing the healing in two groups of animals—one normally saturated with the vitamin and the other supplied with barely enough to maintain reasonable health, referred to as the subscurvy group (Hunt, 1941). In subscurvy animals the wounds in the earlier stages of healing are redder and more swollen, showing an apparent prolongation of the inflammatory phase of healing. Scabs separate later and shrinkage is less. The scars, even at three weeks, are puckered, sunken and discoloured in contrast to the pale, slightly elevated, fine, well-contracted scars in saturated animals. It is only by contrast with the control group that the extent of the defect is apparent. Microscopically the changes are even more evident. Cellular proliferation continues in the subscurvy animals, whereas it ends in the control in two weeks as soon as the scar consolidates. Phagocytosis of damaged tissue is also delayed, even though multinucleated giant cells are more numerous. Serous and blood-stained effusions collect between the opposed surfaces of the wound, opening out the corium from within so that the skin becomes reduced in thickness and appears to lie on poor-quality, œdematous, cellular granulation tissue which contains few capillaries. In every case, healing in subscurvy is not so neat or compact or rapid as in the controls.

The intercellular material shows comparable defects. Silver-staining precollagen appears in both subscurvy and normally saturated animals by the fifth day. In the controls it forms rapidly and soon becomes converted to translucent collagen, the process appearing well advanced by the twenty-first post-operative day. In the experimental animals, by contrast, the silver-staining precollagen collects more slowly and the intercellular substance remains argyrophil in nature. Comparable changes can be seen in healing gastrotomy wounds where phagocytosis of the catgut ligature is delayed in a striking manner.

In 1941 I was able to demonstrate that full scurvy supervening on recently healed wounds had the effect of reversing the process already described, collagen reverting to precollagen in the normally healed wound and precollagen becoming converted to a completely amorphous matrix of no holding power at all in the partially deficient animals, so that one such wound ruptured spontaneously on the thirty-fourth

post-operative day. Pirani and Levenson (1953) have produced additional experimental evidence of this reversion. The part played by the vitamin in this process of healing is one of considerable complexity and not a simple chemical reaction involving only the deposition of collagen.

Attempts have been made to find out if changes comparable to those in guinea-pigs occur in man. It appears that they do, but only in the later stages of deficiency (Lund and Crandon, 1941). To prove the point in man on post-mortem material presupposes a neglect which is not to be contemplated, but early in the war opportunities came for studying such cases. One may be cited as suggestive that subscurvy is of somewhat comparable significance in the human. The patient died on the thirteenth day following operation for a ruptured jejunum. He was shown *post mortem* to be grossly deficient in vitamin C. His wound appeared in many ways similar to that of the subscurvy guinea-pig. A comparable case, dying in similar circumstances on the twelfth post-operative day but saturated with the vitamin, showed sound union throughout the thickness of the corium.

Wound-contraction

At the Royal College of Surgeons, wound contraction is being investigated by the tattoo method devised by Abercrombie *et al.* (1954). The conclusions are that at least two processes are involved, one the contraction of the central granulations and the other an inward movement of the wound edges towards the centre. Contraction begins on the fifth day after wounding and depends upon some substance appearing at the edges of the wound, which causes them to come together in the manner of a draw-string (Grillo *et al.*, 1958). Fixation of the skin and subcutaneous fat to unyielding fascia and periosteum will prevent this drawing-in, as occurs with varicose ulcers. In large perineal wounds, on the other hand, once it has begun, this mysterious force seems to close the gaps we make in a short time, and is one of the facets of wound healing appreciated by proctologists.

A case of such contraction occurred in a patient who had had an abdominoperineal excision of the rectum by Mr. Cecil Joll many years ago. He used to wash out his colostomy and one day, soon after the war, he perforated the colostomy when he accidentally pushed his catheter into the subcutaneous tissues. Within a few hours, a fulminating infective gangrene had developed. I excised it widely, cutting away the end of the colostomy loop with the gangrenous and crepitating fat and skin, leaving a defect about 4 × 3 in. (10 × 7·5 cm), with the open colon in the base of the wound. The fæcal stream was diverted by a transverse colostomy. Fig. 5 shows the condition of the healed wound.

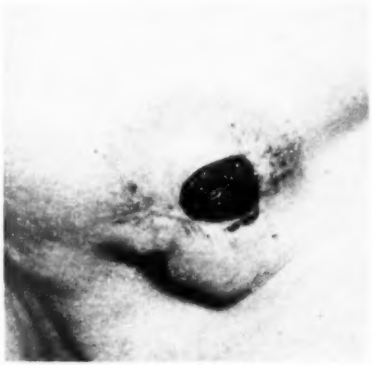

FIG. 5.—Colostomy healed by contraction of granulating wound 4 × 3 in. (10 × 7·5 cm).

Nothing further has been done, except to close the transverse colostomy when the first colostomy wound had contracted down. The edges of skin and fat have moved in, and joined themselves to the edge of the colonic stoma with the minimum of intervening scar.

Regrowth of Muscle

Le Gros Clark (1946) has shown that muscle regenerates best when the severed ends are approximated without an intervening space. The initial fibrous union is replaced over a period of many months with muscle, so that in the end the site of muscle-cutting incisions can hardly be seen.

Effect of Hormones on Healing

This aspect of healing is rightly attracting much attention and I regard its further investigation as urgent. An illustrative case is that of a young, fit man of 20 who arrived in this country suffering from acute appendicitis. An acutely inflamed but not gangrenous appendix was removed without delay and the patient made a good recovery, leaving hospital on the eighth post-operative day. Two days later he was readmitted for acute abdominal pain and fever. A mass had become detectable in the pelvis. It was discovered that he had been taking a preparation of adrenocortical hormone for the previous three or four months in doses equivalent to 75 mg cortisone a day, for an unrelated minor ailment. The drug was stopped. Rest and antibiotics improved him and he left hospital, only to be readmitted on the twenty-first post-

operative day worse than before and with a leucocyte count of 12,000. A large pelvic abscess was evacuated containing fresh blood and old blood clot. The tissues around the abscess were inert, brittle and œdematous. The second wound healed slowly and reluctantly with the aid of blood transfusions, progress being punctuated by secondary hæmorrhages.

If my interpretation of current theories is correct, the cortisone in this case was sufficient to inhibit the orderly organization of blood clot within the appendicular vessels, so that when the catgut was absorbed, hæmorrhage occurred, continued from time to time and the healing process was visibly impeded.

Experimentally it has been shown that cortisone, hydrocortisone, œstradiol and testosterone inhibit the proliferation of fibroblasts and the production of granulation tissue. The earliest stages of wound healing and healing *per primam* are less affected than when clots have to be organized. Fibroblasts fail to develop properly, ill-formed capillaries arrange themselves circumferentially round clots, instead of radially penetrating into them, granulation tissue is defective and the formation of collagen fibrils is inhibited (Taubenhaus *et al.*, 1953).

The pituitary growth hormone and desoxycorticosterone encourage the formation of a granulation tissue which is abnormally luxuriant. The effect of these stimulants may, therefore, also be harmful. It is important to know how much steroid needs to be administered and for how long to produce deleterious effects and how we can best neutralize it. Publication of human cases is needed. Enquiry should be made as to whether patients have received steroids, and if so, they must be treated as if they had a deficiency, however healthy they may appear to be.

This review of wound healing may have appeared disjointed, because each aspect tends to be studied separately. It is difficult to link them all so that they can be traced as one process, yet with an emphasis on their various facets in different types of injury. The impression that I wish to leave with you is that healing is a unity just as much as is inflammation. Last, I have not suggested how much protein or vitamin should be administered, because it must be self-evident that the best nutrition possible should be the surgeon's aim. It is noteworthy that the interval between the operation and the collagen phase provides a breathing space during which full saturation with ascorbic acid can be achieved and at least one part of healing can take place to the best advantage. It is to be hoped that in time it will be possible for all facets of the process to be similarly improved.

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Section of Physical Medicine

President—BASIL KIERNANDER, M.R.C.P.

Meeting
October 14, 1959

DISCUSSION ON NEUROPATHIES IN RHEUMATIC DISEASE AND STEROID THERAPY

Dr. Barbara Ansell (Taplow):

Vascular lesions in muscles and nerves have been recognized by pathologists for some time (Radnai, 1953; Cruickshank, 1954). In 1953 Robinson *et al.* reported 4 patients with rheumatoid arthritis who developed peripheral neuritis with arterial lesions, but it was not until 1957 that a full clinical description of rheumatoid polyneuropathy was made (Hart *et al.*, 1957). Since then other reports have appeared (Irby *et al.*, 1958; Mason and Steinberg, 1958). However, not all patients attending a rheumatology unit complaining of numbness, paræsthesiæ or burning pain in the extremities are necessarily suffering from rheumatoid polyneuropathy, and before describing some typical cases I propose to mention a few diagnostic problems. The patients in this series are under the care of Professor E. G. L. Bywaters at Hammersmith Hospital and the Canadian Red Cross Memorial Hospital at Taplow.

Neuropathy Secondary to Local Pressure

The first group consists of patients with rheumatoid arthritis in whom the swelling and disorganization of joints has caused neurological symptoms and signs by pressure. A common site is the carpal tunnel, so that to the complaint of increased pain and swelling of the affected wrist are added paræsthesiæ and numbness over the distribution of the median nerve. Local pressure may also arise from a large effusion in a joint such as an elbow or knee.

Case I.—A 48-year-old woman who had had arthritis for six years noticed severe pain and swelling of the left elbow, followed by weakness of the left hand and wrist. There was a large effusion in the left elbow with a cystic swelling over the olecranon, sensory loss of ulnar distribution and motor weakness of all muscles supplied by the posterior interosseous nerve. Aspiration of the elbow relieved the neurological symptoms. However, a large effusion recurred a few weeks later, again accompanied by neurological signs. It became impossible to control this effusion by local therapy, and in 1957 treatment with cortisone was started. Within a month the elbow greatly improved, all neurological signs had gone, and the patient has remained in this state for the last two years.

The importance of neck involvement as a complication of rheumatoid arthritis is now well recognized. The sequence of events which may occur is illustrated by the following case:

Case II.—A 60-year-old woman had suffered from severe rheumatoid arthritis for six years when she first noticed paræsthesiæ in the hands. This was followed by increasing pain, suggestive of root involvement, and later weakness of the hands. Suddenly, four months later, she lost all sensation in her hands, although they felt soaking wet. She was admitted to hospital, where examination revealed burn scars and blisters on the fingers; complete loss of heat, cold and pain sensibility in the fingers; absent pin-prick or light touch on the elbows; wasting of the small muscles of the hands; increased reflexes in the arms and an upper motor nerve lesion in the legs which was very like syringomyelia. She had, however, a clear-cut sensory level and X-ray of the neck showed a mobile subluxation of C.3 or C.4.

Neuropathy from Intercurrent Disease

This group is composed of rheumatoid arthritic patients who developed a second disease.

Case III.—A 20-year-old girl in remission from severe Still's disease, which she had had for fifteen years, was admitted with a six-day history of "pins and needles" beginning in the left foot and spreading to the right foot and both hands. Two days later she noticed tenderness and weakness of the legs. In addition to residue of the old arthritis, there was on examination marked tenderness of the calves, weakness of dorsiflexion of the ankles and right wrist, loss of ankle and knee jerks, and stocking anæsthesia to the knees. E.S.R. 11 mm in one hour (Westergren); C.S.F. protein 700 mg%. A diagnosis of infective polyneuritis was made and she rapidly improved with complete recovery in about three months.

Typical peripheral neuropathy in older patients with rheumatoid arthritis can result from carcinoma, diabetes, or pernicious anæmia, or a careful history may reveal exposure to toxic agents.

More localized lesions need to be distinguished from pressure due to a prolapsed disc, or a tumour such as a neuroma. Here differential diagnosis may be complicated by the fact that in rheumatoid arthritis, and more particularly ankylosing spondylitis, the protein in the C.S.F.

can be raised in the absence of any neurological disorder (Ludwig *et al.*, 1942).

Neuropathy and Arthritis Simulated by Other Diseases

Some patients present with aching and paræsthesiæ in the extremities. The causes may vary widely, from Paget's disease with secondary degenerative joint disease and muscle cramps in the legs to diseases which simulate rheumatoid arthritis and can themselves be complicated by neuropathy, e.g. myelomato is (Clarke, 1956) and leukæmia (Sparling *et al.*, 1947). Included in this group are certain endocrine disorders—myxœdema, acromegaly and hyperparathyroidism with bone pain and muscle cramps. Finally, peripheral neuritis from any cause may simulate rheumatoid arthritis with painful, wasted, sweating extremities showing a tendency to ulnar deviation.

Rheumatoid Polyneuropathy

Cases IV to VII represent the varying features seen in rheumatoid polyneuropathy.

Case IV.—A man, aged 40 in 1941 when seen with typical nodular rheumatoid arthritis. Initially he received gold therapy, causing dermatitis, later phenylbutazone which produced dyspepsia, so in 1956 he was admitted to hospital for maintenance steroid therapy. One month prior to admission he developed purpura on both legs which recurred over the next few weeks. Two months after commencing prednisolone he had tingling followed by numbness over the distribution of the right peroneal nerve, and a month later the left side was similarly affected. At this time he had large effusions in both knees. Following aspiration there was some improvement in the paræsthesiæ although the numbness persisted and this was thought to be a pressure lesion. He did well for the next eighteen months and was able to bicycle to work, but then numbness and tingling in the left foot returned followed by sciatic pain and foot-drop. Two weeks later there was extensive purpura on the legs, bleeding from the bowel and a rise in blood pressure. His subsequent course has been downhill and he has developed congestive cardiac failure. L.E. cells have never been found and the D.A.T. (Scott, 1952) has always been strongly positive.

Case V.—A man of 56 whose arthritis, commencing in 1956, was so severe that within a year he was almost bedridden. He was given prednisolone and remobilized, but nine months later subcutaneous nodules appeared. Seven months after this cutaneous lesions were first seen and he developed pain and paræsthesiæ in the right foot. More recently he has noticed numbness and coldness of the second and third fingers of his right hand. An arteriogram revealed blockage of the digital vessels of the second and third right fingers. Biopsy of one of the cutaneous nodules showed collagen degeneration and vasculitis. The D.A.T. is positive, no L.E. cells have been seen and no cryoglobulins have been detected. In this case of typical rheumatoid arthritis of short duration prednisolone did not prevent the development of nodules or arteritis.

That this vasculitis does involve the nerves has been seen in a post-mortem section of a sciatic nerve which showed an obliterated vessel with thickened intima; the patient, a girl, died of peritonitis while on maintenance steroid therapy, some seven years after the onset of a severe nodular rheumatoid arthritis. However, at no time had she symptoms or signs relevant to this.

Case VI.—A woman, aged 67, suffering from typical nodular rheumatoid arthritis for fourteen years which was treated conservatively suddenly developed a right foot-drop. Three weeks later with equal suddenness she had a left foot-drop and numbness of the fourth and fifth fingers of the right hand. At this time cutaneous nodules and nail-fold lesions were present; the bilateral foot-drop was associated with loss of ankle-jerks and impairment of sensation to pinprick on the leg and along the ulnar distribution of the right hand. Investigations showed a marked delay in reactive hyperæmia of the legs, D.A.T. positive at 1 : 256, positive antinuclear factor and an occasional L.E. cell in the peripheral blood. In spite of the last two findings, the absence of other visceral lesions and the general pattern of her disease were suggestive of rheumatoid arthritis with vascular involvement.

Case VII.—A man, aged 41, developed palindromic rheumatism in 1949. Residual joint involvement, olecranon nodules and a positive D.A.T. were present in 1957. He received prednisone but because of abdominal colic this was stopped one month later and large doses of salicylate given. He developed purpura, a rash and severe arthritis; as his abdominal symptoms had improved he was restarted on prednisone. Shortly afterwards he developed a right peroneal nerve lesion and at this time, in addition to nail-fold lesions, chest X-rays showed transient bands of linear collapse. Subsequently the left ulnar and four months later the right median nerve became involved. Histology of the skin rash showed typical polyarteritis nodosa. He has continued on steroid therapy and has made a slow recovery from the neuritis, with persistent wasting of the right hand but only minor residua in the joints. This patient would seem to have mild rheumatoid arthritis and true polyarteritis nodosa.

Neuropathy must now be included as a manifestation of rheumatoid disease. It tends to affect older patients with long-standing rheumatoid arthritis who have nodules, a positive D.A.T., and often cutaneous nodules, nail-fold lesions or purpura. The ætiology is probably vascular and it has been suggested that it is due to blocking of small vessels by macroglobulins. The role of steroids in its production is uncertain. Neuropathy can occur in patients not on steroid therapy (Hart *et al.*, 1957), and only 4 of the 10 patients with vascular lesions reported by

Bywaters (1957) had received steroid. Once neuropathy is present their use does not seem to aid recovery. The apparent greater incidence of neuropathy in patients on steroid may be merely a manifestation of the severity of the underlying disease.

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Dr. F. Clifford Rose (London):

Peripheral neuropathy is a clinical term signifying an affection of peripheral nerves and embracing the multiple symmetrical type, both acute and chronic, and "mononeuritis multiplex". The presenting symptoms include numbness or tinglings in the hands and feet, clumsiness of the hands, and difficulty in walking. Examination characteristically shows weakness and wasting of the distal musculature with loss of tendon reflexes and sensory loss of glove-and-stocking distribution. The diagnosis of the symmetrical type of polyneuropathy is usually easy and the differential diagnosis, from the rheumatologist's point of view, was discussed by Dr. Barbara Ansell.

The syndrome of mononeuritis multiplex occurs when individual nerves are affected, producing an asymmetrical clinical picture. Since Gowers (1888) first grouped peripheral neuropathies into multiple and isolated forms, this division has been useful in differentiating pathogenesis. Mononeuritis multiplex is certainly common in polyarteritis nodosa and is due to infarction of the larger peripheral nerves because of involvement of their nutrient arteries. Some other causes are collagen disease, diabetes, sarcoidosis, alcohol, serum sickness, neuralgic amyotrophy and barbiturate poisoning, and it is a common presentation in leprosy. Mononeuritis multiplex following serum sickness may have a vascular basis as spasm of the vessels characteristically occurs. Neuralgic amyotrophy is related and often occurs post-operatively beginning with a severe pain across the back of the shoulders followed within a fortnight by brachial palsies. A few cases following barbiturate intoxication have been recorded (Brunnschweiler, 1941).

In distinguishing peripheral neuropathy from other causes of muscle weakness, electromyography often proves useful. Spontaneous fibrillation is marked in polyneuritis and the motor units, which are reduced in number, are increased in duration and may be increased in size. The nerve threshold is raised and, most significant of all, the conduction velocity is slowed.

Pathologically, the neurons that make up the peripheral nerve can be affected in any part of their course, including their extension into the spinal cord. Swelling and breakdown of the myelin sheath is followed by phagocytosis leaving empty Schwann tubes. The axis cylinders may also be affected but with recovery they regenerate and the myelin sheath is completely re-formed. Degeneration is greater towards the distal end of the fibre, and the earliest demonstrable change is in the terminal twigs. There is thus a "dying back" of the neuron (Greenfield, 1958), and this is not surprising since the maintenance of the axon depends on the nutritive power of the cell nucleus. Thus the first symptoms occur in the hands and feet which are supplied by the longest axons in the body.

Although from the histological point of view, the neuron can react only in a limited number of ways, the alterations in metabolism are more numerous. The best understood abnormality is the failure of oxidation of pyruvic acid which is formed by the breakdown of glucose in the Krebs' cycle. This is probably the mechanism in alcoholic neuropathy as well as the neuropathy due to thiamine and pantothenic-acid deficiency. Abnormalities of glucose catabolism are not often found clinically. Analysis of the case notes of in-patients diagnosed as having peripheral neuropathy at the National Hospital, Queen Square, in the last four years, is shown in Table I.

TABLE I.—PERIPHERAL NEUROPATHY (80 CASES)

Sex Incidence
Male: 47
Female: 33

Age Incidence

Age in years	20	21–30	31–40	41–50	51–60	61–70	70
No. of cases	3	6	7	21	21	18	4

This is a highly selected series, as a neurological hospital will attract the more difficult problems and the respiratory unit brings in a considerable number of the acute Guillain-Barré type. In 13 patients in whom the pyruvate tolerance was

estimated, it was abnormal in only 2. Interestingly enough, one of these was an alcoholic who improved after treatment, the pyruvate tolerance then returning to normal.

80% of the patients were over 40 years of age, and there was a preponderance of male to female in the proportion of 3 to 2—points of some importance when considering the corresponding incidence in peripheral neuropathy due to collagen disease.

Steroids have been considered a cause, as well as a treatment, of peripheral neuropathy. Of the 80 patients in this series, 27 fell into the acute Guillain-Barré type. Of these, 9 were given steroid therapy, and all made a good recovery. However, of the 18 who were not given steroids, 16 made a good recovery, and the value of steroid therapy is therefore impossible to assess from these figures. Of the 9 chronic cases who were given steroid therapy, only 2 improved, and again, although the value of steroid therapy is in doubt, there was no evidence that any were made worse.

As to the possibility of steroid-induced neuropathy, it should not be forgotten that in the past many drugs have been implicated; the number listed in a current textbook of neurology being more than 60 (Brain, 1955). Yet it is only in a few cases that a cause is identified. Table II

TABLE II.—PERIPHERAL NEUROPATHY (80 CASES): ÆTIOLOGY

Diabetes	8
Alcoholism	7
Post-influenza	6
Carcinoma	3
Amyloid	3
Familial	3
Vitamin deficiency ..	3
? Polyarteritis nodosa ..	1
Scleroderma	1
Unknown	45

shows that of the 80 cases in this series, in 45 no cause was found. This proportion is identical with that given by Elkington (1952).

Only 2 of this series could be considered due to collagen disease; the case of scleroderma is being fully reported elsewhere.

Of particular interest was the case called in the table—for want of a better term—? polyarteritis nodosa:

A man aged 51, admitted under the care of Dr. Hamilton Paterson in February 1959. At the age of 36 he developed rheumatoid arthritis. He responded to gold treatment for about six months, then relapsed and the characteristic fluctuant course of rheumatoid arthritis ensued. Two years ago, owing to a more severe relapse, prednisolone, 20 mg daily, was given, but this was soon reduced to 10 mg daily. Although he continued to have pain, he remained at work as an insurance agent. In October 1958 he noticed aching of the backs of the legs, followed one month later by numbness in the same distribution. In December, his feet became weak over a period of ten days, and he was unable to walk. In January 1959 he was not able to sit up and he noticed numbness and weakness of the left hand, followed a few weeks later by the same symptoms in his right hand.

On examination.—Extremely ill, flushed and dehydrated. Disorientated and occasionally delirious. No abnormality in cranial nerves. Gross wasting of limbs with marked flaccidity. The movements of his shoulders, elbows, hips and knees were moderately weak, but there was complete paralysis distally, and he could not move wrists, fingers or feet. All his tendon reflexes were absent and he had anæsthesia to all sensory modalities up to his knees and elbows. Over the shins and heels were infected ulcerative lesions. His hands showed the typical appearance of rheumatoid arthritis.

Investigations.—X-ray of the hands showed osteoporosis, loss of joint space and peri-articular erosions. Hæmoglobin 79%; W.B.C. 13,000/c.mm (polys. 86%, lymphos. 14%). E.S.R. 57 mm in one hour (Wintrobe). Urine: no albumin, red blood cells or casts. Electrophoresis of the serum proteins showed a slight increase in the α_2 globulin. He was considered to be too ill for further investigation, and a muscle biopsy was not done.

He was treated with an intravenous drip of hydrocortisone and the oral prednisolone was increased to 20 mg t.d.s. Following this, his general condition improved, but the ulceration of his legs increased and his toes blackened. Six weeks after admission, he deteriorated rapidly and had difficulty in swallowing. A tracheostomy was performed and he survived another two months.

Here was a 51-year-old man with a fifteen-year history of rheumatoid arthritis, who, after two years of steroid therapy, developed an extremely severe, rapidly progressive peripheral neuropathy. Although polyarteritis nodosa was seriously considered as a possible diagnosis he had no hypertension or eosinophilia and there was no evidence of cardiac, pulmonary or renal involvement.

Post-mortem examination revealed no evidence of polyarteritis nodosa, but many of his blood vessels showed grossly thickened intima (Fig. 1). There was no evidence of panarteritis or cellular infiltration but the lumen was nearly occluded by the intimal proliferation. Similar changes were seen in blood vessels elsewhere.

This case raises the questions of the relationships of the neuropathy to the vascular lesion and of the vascular lesion to rheumatoid arthritis and steroid therapy.

From the evidence of polyarteritis nodosa, it seems reasonable to suggest that the neuropathy is ischæmic in origin. Hart *et al.* (1957) reported 10 cases of rheumatoid neuropathy and considered that diffuse arteritis was the best explanation for this complication.

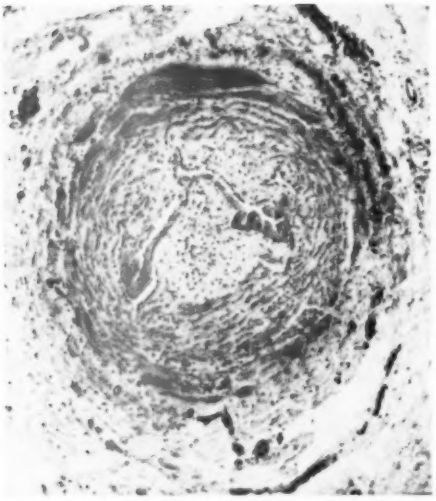

FIG. 1.—Vessel from right toe. (H. & E. ×41.)

Peripheral neuropathy occurs in about 50% of cases of polyarteritis nodosa and in Lovshin and Kernohan's series (1948) half their cases were classified as symmetrical and half as "mononeuritis multiplex". In systemic lupus erythematosus the incidence is under 3%, and in rheumatoid arthritis it is even less. In 1953, however, several cases were reported of neuropathy occurring in patients with rheumatoid arthritis who had been treated with steroid therapy (Levin *et al.*, 1953; Robinson *et al.*, 1953). Although this was correlated with vascular disease, the arterial lesions differed qualitatively from those of polyarteritis nodosa, "particularly with respect to their distribution, lack of regional involvement and usual absence of necrotizing arteritis" (Robinson *et al.*, 1953). In a series of 75 autopsied cases of rheumatoid arthritis, none of whom had received steroid therapy, Cruickshank (1954) found evidence of involvement of the blood vessels in 18, the peripheral nerves being affected in 5. This type of arteritis was again distinguishable from polyarteritis nodosa. Hart *et al.* (1957) wondered whether arteritis occurred more commonly in steroid therapy since 3 of their cases manifested neuropathy within one month of discontinuing this treatment. Kemper *et al.* (1957) found that vascular lesions in rheumatoid patients were more common in those with hypercortisonism, but the arteritis in their cases was of the necrotizing type.

10 cases of rheumatoid arthritis with vascular lesions were reported by Bywaters (1957) but as only 3 of these had had cortisone he thought that the drug did not play an important part in their production. He also pointed out that the vascular lesions of intimal proliferation without panarteritis were not specific for rheumatoid arthritis.

There is some evidence that steroid therapy does affect blood vessels, possibly by its effect on cholesterol metabolism, e.g. there is increased deposition of lipid in the intima and media of leukæmic patients who have had steroid therapy (Etheridge and Hoch-Ligeti, 1952).

Cortisone and its newer derivatives are often given to the more severe, long-standing cases of rheumatoid arthritis and it is these cases that are the most likely to develop neuropathy.

Six years ago, Robinson *et al.* (1953) reported 4 cases of rheumatoid neuropathy which they correlated with severe diffuse arterial pathology. Although three of their patients had had steroid therapy, they stated that "no definite conclusion with respect to the role of hormonal therapy in the development of these lesions and their clinical manifestations seemed justified".

Arteritis and neuropathy both occur in untreated rheumatoid arthritis. Whether there is an increase in these sequelæ since the advent of steroid therapy is difficult to prove, although it is possible that the type of vascular lesion differs in the treated cases.

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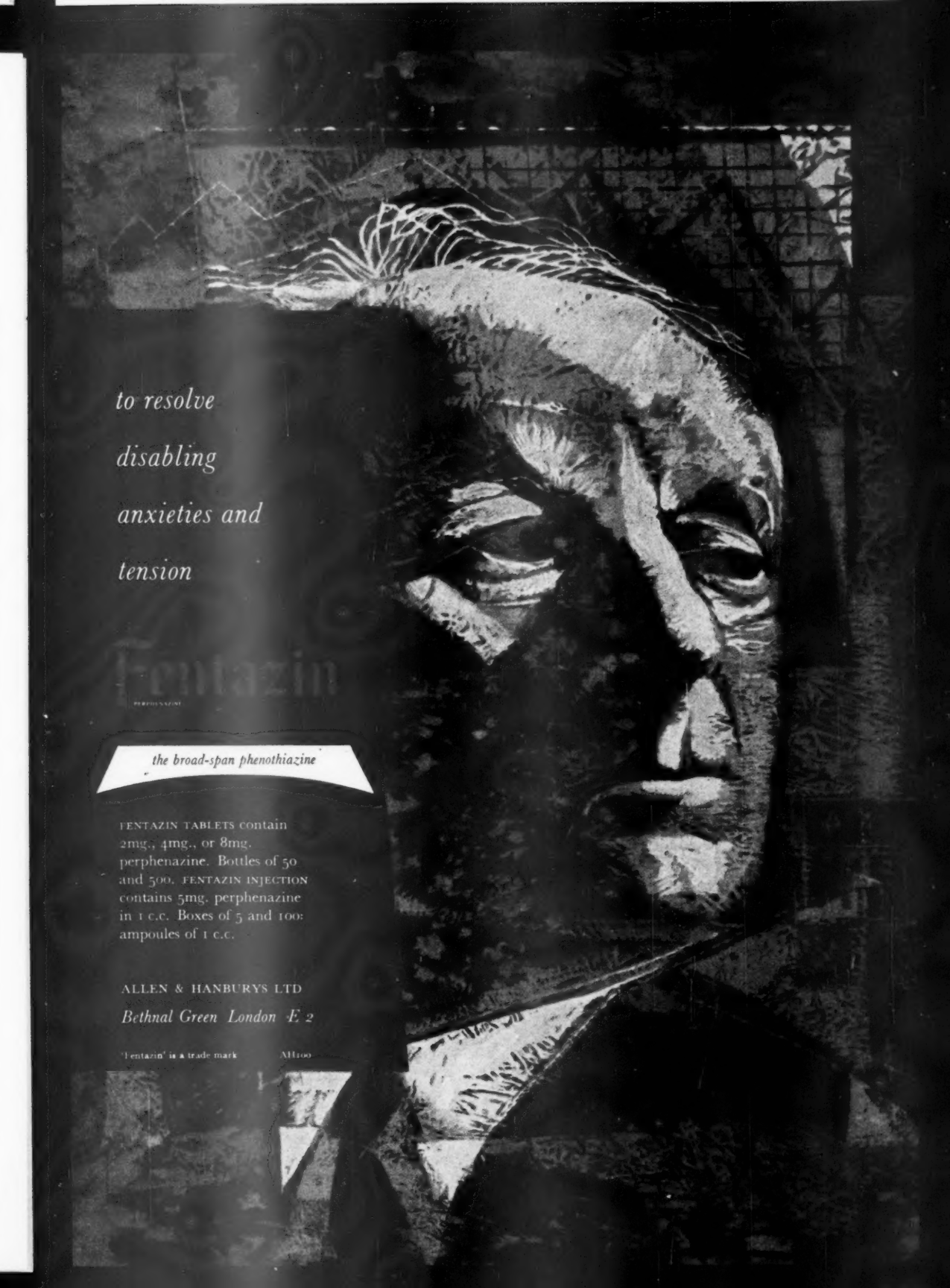
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Section of the History of Medicine

President—CUTHBERT E. DUKES, O.B.E., M.D.

Meeting
October 7, 1959

Mr. W. J. BISHOP read a paper entitled **Some Historical Cases of Autosurgery.**

Meeting
November 4, 1959

"Sir" John Hill, M.A., M.D. (1706-1775) Apothecary, Botanist, Playwright, Actor, Novelist, Journalist

By A. D. MORRIS, M.D.
Peterborough

"I do remember an apothecary,
And hereabouts a'dwells, which late I noted
In tatter'd weeds, with overwhelming brows,
Culling of simples; . . . . . ."

JOHN HILL belonged to the lowest order of medical men—the apothecaries. An egregious character, he unfortunately cultivated "the gentle art of making enemies", antagonizing the scientific men of his own age and prejudicing those who came after. To-day he is recognized as one of the pioneers of the science of botany in this country.

At one time, tired of being a struggling apothecary, he tried playwriting and acting, and failed at both. A natural bent for botany and a life-long love of the science eventually led him to the remunerative position of superintendent of botanical gardens. He also cultivated, successfully and profitably, his own herbal garden.

Hill had a flair for writing and was a prolific author. Though an undistinguished playwright, he achieved immediate success writing scientific works, mainly on botany, but also on geology and fossils, which at that time included mineralogy and palæontology. A few of his botanical works were written in the universal language of science, Latin, but most were in English, an innovation which had an immediate appeal to the laymen who were eager for scientific knowledge, especially botany, the most popular of all the natural sciences. He was soon overwhelmed with offers from publishers, and seemed capable of writing on almost any subject. He even descended to popular journalism, editing a periodical and writing a daily column for a newspaper.

When he became unpopular with the public and the sale of his books dropped, he returned to the apothecary shop. Well aware of the value of advertising he wrote numerous articles extolling the virtues of certain herbs, which he not only grew in his own garden, but prepared and sold in his shop.

Other than a record of baptism at the parish church of St. John Baptist, Peterborough, on February 4, 1707, little is known of Hill's early years. His grandfather, his father, and his elder brother were clergymen of the established church and graduates of Cambridge University. His father, Theophilus Hill, was a minor canon of Peterborough Cathedral. It is not known how or where John Hill was educated, but he must have received at least a sound classical education for he had a good knowledge of Greek and Latin.

He was a born rebel. He ran away from home, "having voluntarily banished himself from the austerities of an over-rigid father". In 1732 he was apprenticed to an apothecary, in the City of Westminster, but there is no record that he completed his apprenticeship or received the freedom of the Apothecaries Company.

Five years later, he opened an apothecary shop in St. Martin's Lane in the Covent Garden district. Henry Woodward, the celebrated comedian, said the shop was little more than a shed, and we learn that Hill, "having started business for himself on the humblest scale, learned what it means to be without the bare necessities of life".

To the precarious finances of an apothecary shop he added an equally impecunious wife and was soon looking for a means to supplement his income.

He had been in practice only a year when he wrote the libretto of an opera, "Orpheus" (1738),

which he submitted to John Rich, well known as a theatrical manager. Rich rejected it, but in the following year produced an opera entitled "Orpheus and Eurydice" and immediately Hill accused him of plagiarism. Angry and indignant, he attacked Rich in a preface to his "Orpheus" which he had published, giving public vent for the first time to the hatred and vindictiveness which plagued him for the rest of his life. Rich became the first of a long succession of enemies.

At the Chelsea Physic Garden, Hill met many aristocratic and wealthy patrons of botany who were much impressed with his botanical knowledge. In 1743 the Duke of Richmond engaged him as superintendent of the botanic gardens and museum at Rook's Hill, Goodwood. Later he acted in a similar capacity for Lord Petre.

While thus employed he conceived a scheme for supplying specimens of uncommon plants to the then numerous collectors, travelling extensively in search of rare specimens which he dried and preserved by a special process of his own. The Duke of Richmond and Lord Petre gave him every encouragement and financed the scheme, but though Hill worked hard he failed to make a profit, and the project was abandoned.

He did not return to pills and potions, but decided to become an actor. Seeking immediate applause and adulation he insisted on roles much too difficult for a beginner, and was a dismal failure. This was a great blow to his pride, as well as his pocket, and he became so embittered that the actor-managers, John Rich, Henry Woodward, and later David Garrick, found themselves victims of vicious, and sometimes malicious, attacks.

Once again Hill opened a shop, this time in Broadway, Westminster, obtaining an appointment as apothecary to General Anstruther's regiments which were quartered in the Savoy. He could now resume his scientific studies, and began by translating Theophrastus' "History of Stones". The book was published in 1746, the Greek text printed side by side with the English translation. It was well received and Hill's reputation as a naturalist and author was finally made.

He was asked to write a supplement to Chambers' Cyclopædia and at the same time became editor of a new periodical *The British Magazine*, which he edited from its inception in 1746 until publication ceased in 1750. Following this he wrote a daily letter, signed "The Inspector", for the *London Advertiser and Literary Gazette*, and became a forerunner of the present-day gossip writers.

Despite his journalistic commitments he found time to embark upon a voluminous work on natural history entitled "A General Natural History" (1748–1752), consisting of three folio volumes: "A History of Fossils", "A History of Plants", and "A History of Animals". This work contains a great deal of originality, e.g. the first attempts to classify the animalcules. now called the Infusoria and to distinguish fossils from minerals. It was he who suggested for the petrified remains the terms extraneous and adventitious which James Parkinson in his "Organic Remains of a Former World" adopted.

For Hill success was now followed by a financial security he had never known. He moved into a large house surrounded by several acres of gardens, now Lancaster Gate, and married his second wife, the Hon. Henrietta Jones, sister of Charles, fourth Viscount Ranelagh.

His income as a journalist was £1,500 a year, which, said a biographer, "is three times as much as ever was made by any writer in the same period of time". He spent as fast as he earned. It was important to him that his carriage and horses were the smartest in town and he the most fashionably dressed man of quality in an age of resplendent attire. He went everywhere, most conspicuously to the front row of the stalls, particularly when royalty was in attendance.

He mixed with the nobility, was received at Court, and as a man about town frequented the coffee houses and taverns where he picked up the gossip and scandal which enlivened his newspaper articles. Once humble and reticent he emerged, vain, boastful, quarrelsome and spiteful. The slightest affront released a torrent of envenomed abuse, which, however, often produced a flood of equally vituperative public replies.

By 1750 his stature was such that he received the degrees of M.A. and M.D. from the University of St. Andrew's. George Pile, M.D., L.R.C.P., recommending Hill for the honours, wrote "This gentleman is well known to the learned world for his General and Natural History of Animals, Vegetables and Minerals, likewise for his Translation and Commentaries on Theophrastus' History of Stones, &c. I am, Sir, persuaded that this gentleman will be an Ornament to Our Profession."

He tried desperately to become a Fellow of the Royal Society, and his publishers pressed for the addition of the distinguished initials, but although Hill asked George Lewis Scott to propose him he could not get a single additional signature. He retaliated by calling the entomologists butterfly hunters; the conchologists cockleshell merchants; and the antiquarians medal scrapers. "There is no doubt", wrote Professor

T. G. Hill, "that his claims to the Fellowship on scientific grounds were as strong as any and stronger than most of the Fellows, and Hill, who was by no means lacking in self-confidence, knew this." Hill attacked the society in two publications "A Dissertation on Royal Societies" (1750) and "A Review of the Works of the Royal Society" (1751). In the latter work the print and arrangement of the pages were a replica of those in the *Philosophical Transactions*. However, his satire was mixed with sound critical advice. Surprisingly the Council of the Royal Society eventually acted on his criticisms, appointing a committee of five Fellows to scrutinize all papers submitted to the *Philosophical Transactions* and deciding that the Society itself would in future publish the *Transactions*. "Sir John Hill, this despised man", wrote Isaac D'Israeli, "performed more for the improvement of the *Philosophical Transactions* than any other contemporary." In Hogarth's well-known picture, "Beer Street", a companion to "Gin Lane", is a basketful of books, one of which is inscribed "Hill on Royal Societies".

George III asked Dr. Johnson what he thought of Dr. Hill. "Johnson", said Boswell, "answered that he was an ingenious man but had no veracity . . . he had seen objects magnified of a much greater degree by using three or four microscopes than by using one. 'Now', added Johnson, 'everyone knows that the more of them he looks through the less the object will appear.' 'Why', replied the King, 'this is not only telling an untruth but telling it clumsily; for, if that be the case, everyone who can look through a microscope will be able to detect him.' 'I now', said Johnson . . . 'began to consider that I was depreciating this man in the estimation of his sovereign, and thought it was time for me to say something more favourable.' He added, therefore, that Dr. Hill was notwithstanding, a very curious observer; and if he had been content to tell the world no more than he knew he might have been a very considerable man, and needed not to have recourse to such mean expedients to raise his reputation."

Johnson clearly knew nothing about microscopes, since by microscopes Hill meant lenses. "If Hill's reputation for lying rests on no surer foundation than this", Professor Hill remarked, "He must be acquitted of much that is charged him. . . . This is the more to be regretted since the opinion of a man of Johnson's rank, who was contemporary with Hill, might have biased the judgment of smaller and lesser men."

Hill wrote two plays, both farces, "The Critical Minute" (1754) and "The Rout" (1758). "The Rout" was staged by David Garrick at Drury Lane Theatre, the performance being in aid of a charity, and it was received politely but without enthusiasm. The author's name was not disclosed. Hill, hearing that Garrick did not propose to repeat the performance, circulated anonymous leaflets saying that it had been discontinued because of the indisposition of a leading member of the cast, but when Mrs. Kitty Clive was free to take up the part the farce would be revived. The leaflet stated that the play had been written by a man of quality. The public soon learned that the author was Hill and that the statements in the leaflet were untrue, but Hill prevailed upon Garrick to put the farce on for a benefit performance, the proceeds of which would go into his own pockets. Garrick unwisely agreed, and on this occasion the play was "hissed and hooted". Hill, frustrated once again, blamed Garrick for its failure and opened an outrageous attack on the actor, eliciting a terse and cutting epigram in reply:

> "For Physic and Farces, his equal there scarce is;
> His Farces are Physic, his Physic a Farce is."

By this time, his publishers dared not risk Hill's unpopularity and asked him to write either anonymously or under a pseudonym. His income declined, yet he was still living beyond his means —it was said he "was in a chariot one day and in jail the next". Once again he returned to the pestle and mortar and opened an apothecary shop, this time in fashionable St. James' Street.

His shop served for the sale of his books, as well as the herbal remedies he prepared himself from the herbs grown in his garden at Bayswater. In order to boost their sales he published a number of tracts in which he recommended certain herbs for particular diseases. At the end of one of these tracts is an advertisement listing many of his books and tracts, with their prices, in which it is stated that, "Any of these may be had of the Author at his house in St. James' Street where a bookseller attends to deliver them. Also all Dr. Hill's medicines."

Hill saved the life of "a poor, ugly, old gypsy woman, unpitied and unprotected" who, though innocent of the crime with which she was charged, was found guilty and sentenced to death. It was an exciting case and has been dramatized as a radio play.

Elizabeth Canning, aged 18, an epileptic, suddenly disappeared. A month later she returned home with a strange story. While walking through the City late one night she was seized by two ruffians, who robbed her and struck her a violent blow on the head which brought on a fit. She awoke in a dazed condition to find herself in a room confronted by two women, one old, the other young. The old

FIG. 1.—Sir John Hill, M.D. John Hill was not a Knight (Riddarë) of the Swedish Order of the Polar Star, as was Linnæus, but of the lesser Order of Vasa. The Hon. Lady Hill said that her husband was nominated the first Superintendent of Kew Gardens but there is no evidence that he ever occupied that position. The plant depicted above the portrait belongs to the genus *Hillia* (*Hillia parasitica*), named after Hill by the French botanist, Jacquin.

The engraving was made in 1799 from a portrait in oils painted in 1757.

The Chequer'd World's before thee—go—farewell
Beware of Irishmen—and Learn to Spell.

Behold the Dame, whose chiromantic Pow'r,
Foretells th'auspicious, or th'unlucky hour,
And warns the world, what wonders may befall,
To H—ll* to Virtue or to Justice Hall.

*A Great House in Cheapside.

FIG. 2.—The lines of verse, above the caricature of Hill and the old gypsy woman whom he saved from the gallows, were written by Christopher Smart, the poet, in "The Hilliad", a mock epic poem. Hill had been thrashed in public by a fellow-writer, an Irishman named Brown, whom he accused of not being able to spell properly. This incident is illustrated in the top right-hand corner, whilst in the top left corner is shown the residence of the Lord Mayor, the Mansion House.

woman tried to persuade her to become a prostitute and when she refused, ripped off her stays with a knife and locked her in an attic. Eventually the girl loosened some boards nailed over the window and escaped. From her description the house was easily recognized as a notorious house of ill-fame at Enfield. Elizabeth Canning was taken back there by the police and identified a gypsy as the old woman who had ripped off her stays. A younger woman, Virtue Hall, said she had witnessed the proceedings.

The gypsy was tried for the theft of the stays, found guilty, and sentenced to death in spite of the fact that three witnesses confirmed she was in Dorset at the time of the crime.

Hill in "The Inspector" said that he doubted Elizabeth Canning's story which he declared was "absurd, incredible, and ridiculous." The Justice, Henry Fielding the novelist, on the other hand, declared in the *Covent Garden Journal* that he fully believed the young girl. Hill published a tract, "The Story of Elizabeth Canning Considered. With remarks on what has been called a Clear State of her Case by Mr. Fielding"; in which he countered Fielding's arguments.

The Magistrate and Hill, who was then a J.P. for Westminster, interrogated the witness Virtue Hall whose evidence had convicted the gypsy and persuaded her to admit on oath that the evidence she had given at the trial was false. Elizabeth

Canning was tried for perjury, found guilty, and sentenced to seven years' transportation.

The case was the talk of London. Popular feeling was all on the side of Elizabeth Canning and the Lord Mayor was stoned by the mob.

While Hill's literary machine was turning out book after book, many of them "ghosted", he wrote a popular book on astronomy and "A Naval History of Britain" (1756). When his conscience stirred him he wrote "Thoughts Concerning God and Nature" (1755), a reply to a notorious freethinker, Henry St. John, Viscount Bolingbroke. Hill said that he paid all the expenses of its publication and that it led to his ruin.

His "Essays in Natural History and Philosophy" (1752) contains a description of the animalcules, the Infusoria, as seen under the microscope. The "British Herbal" (1756) is not a "herbal" in the old sense of the term, for it contains a description of all plants and trees found in this country at that time. It is written in English and is notable because it mentions, for the first time in this country, the Linnæan system of classification of plants. "*Flora Britanica*" (1760), however, is written in Latin, and for the first time in a botanical work published in this country the plants are arranged under the Linnæan classification and given the Linnæan names, though the binomial nomenclature is not maintained throughout the work. In "Eden, or a Compleat Body of Gardening" (1757) and "The Gardener's New Kalendar" (1758), both popular books on gardening, the Linnæan system is explained simply and intelligibly.

"The Sleep of Plants and Cause of Motion in the Sensitive Plant" (1757) is written in the form of a letter to the illustrious Linnæus. It is an interesting study in plant physiology, an account of the author's experiments on the effect of light, darkness and touch on the *Mimosa sensitiva* and *abrus*. In his "British Herbal" Hill severely criticised Linnæus' system which he condemned as artificial and unnatural, but in "Eden" he gave Linnæus unstinted praise for bringing order out of chaos.

Two medical works, "The Fabrick of the Eye" (1758), written anonymously, and "The Construction of the Nerves. By Christian Uvedale, M.D." (1758), are attributed to Hill. "A History of the Materia Medica" (1751) is a comprehensive work, a quarto volume of nearly a thousand pages dedicated to Dr. Richard Mead.

"Hypochondriasis; a Practical Treatise on the Nature and Cure of that Disorder, commonly called the Hyp and Hypo" (1766) is worth reading. "To call the Hypochondriasis a fanciful malady", says the author, "is ignorant and cruel. It is a real and sad disease." "Among particular persons," he observes, "the most enquiring and contemplative are those who suffer most by this disease, and of all degrees of men the clergy. I do not mean the hunting, shooting, drinking clergy . . . but the retir'd and conscientious; such as attend in midnight silence to their duty."

One of the most enthusiastic botanists in Hill's time was the Earl of Bute, afterwards Prime Minister, a generous patron who was called "the Mæcenas of Botany". He had a good opinion of Hill's botanical achievements and, having a great influence over George III, obtained for Hill the position of superintendent of the gardens at Kensington Palace. Lord Bute then persuaded Hill, much against his will, to write a work on botany which would be "the most voluminous, magnificent, and costly work that was ever attempted". He assured Hill that he would bear all the expenses of its publication and would indemnify him against any losses incurred from its sale. The first of the 26 folio volumes of "The Vegetable System", as it was called, appeared in 1759 and the last in 1775. It contained 1,600 plates with over 26,000 figures, and the engravings, which were made from drawings done by Hill himself, were said to have cost over £6,000. Lord Bute, after a disastrous year as Prime Minister, retired to Scotland and failed to carry out his obligations, with the result that Hill found himself heavily in debt.

From 1760 onwards, though still employed at Kensington Palace, Hill acted as superintendent of the gardens of the Dowager Princess of Wales at Kew House. There, encouraged by his patroness, he carried out the experimental work on the growth of trees which he described in his book "The Construction of Timber" (1770). It is illustrated with transverse sections of trees as seen through a new variable microscope of his own design. The cutting machine which Hill claimed could cut sections of 1/2,000 of an inch must be one of the earliest known microtomes. The "sliders" he used were of talc, but at the suggestion of the Princess he changed to glass slides. In 1768 he published "*Hortus Kewensis*" in which he described and illustrated some 2,500 plants grown in the Princess's garden. It is probable that Hill assisted in laying out the Royal Botanic Gardens at Kew in 1760.

In the last few years of his life Hill, tormented by the gout, was a very sick man. He struggled to complete "The Vegetable System", but the last volume, published after his death, was unfinished.

In 1774 the King of Sweden, a keen botanist,

invested him with the Order of Knighthood of the Illustrious Order of Vasa. Hill thereafter styled himself Sir John Hill and seemingly no one disputed his claim to the title. In the registers of the aristocracy he is recorded as "Sir John Hill", and even in Debrett (1809) he appears as "the late Sir John Hill".

Time has shown that Hill was right in criticizing the Linnæan system of classification as unnatural. In doing so he was a hundred years in advance of his time. The artificial system has now been replaced by a natural system of classification first introduced by de Jussieu at the beginning of the last century. Hill, however, prophesied that the Linnæan system would live even if a natural system should eventually be established.

The authors of "Makers of British Botany" (1913) and "Pioneers of Plant Study" (1928) have recognized John Hill as one of the founders of scientific botany in this country.

His greatest enemies could not deny that Hill was a man of considerable natural abilities who had an amazing capacity for hard work. One cannot help feeling compassion for this unfortunate man who so often misapplied his talents and who was, after all, his own worst enemy. His particular ability, however, will never be forgotten because John Hill belongs to the history of botany.

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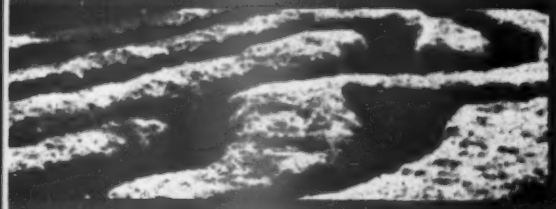

STREPTOMYCIN GLAXO

Section of Orthopædics

President—DAVID TREVOR, M.S.

Meeting
October 6, 1959

Infantile Cortical Hyperostosis of Caffey (Two Cases).—A. BENJAMIN, F.R.C.S., and R. G. SMITH, F.R.C.S.

Since infantile cortical hyperostosis was first described as a new syndrome by Caffey and Silverman in 1945 over 50 cases have been reported. In this paper 2 further cases are presented. The first illustrates the serial radiographic changes which end in spontaneous recovery. The second is of interest owing to its onset during an allergic reaction following an insect bite. The discussion includes a summary of the main features of the disease.

Case I.—A mongol baby was admitted to Hospital when 5 weeks old because he was miserable, did not take his feeds well and did not move his right upper limbs.

Examination revealed a bony hard enlargement of the right scapula with no signs of inflammation. Temperature 98° F, Hb 12·6 g%, W.B.C. 7,000, W.R. and Kahn negative. Radiographs showed an enlarged right scapula due to considerable new bone formation (Fig. 1). The possibility of sarcoma was considered but biopsy showed exuberant growth of reactive subperiosteal new bone (Dr. J. H. Shore).

For a week the mass grew larger. Radiographs showed the shadow of the scapula increasing in size and density (Fig. 2). After one month the increase in size was maintained but the density was decreasing (Fig. 3). After six months the scapula had returned to almost normal size and structure both clinically and radiologically (Fig. 4).

Case II.—A Persian female child aged 7 weeks was admitted to hospital on 17.7.59 with marked

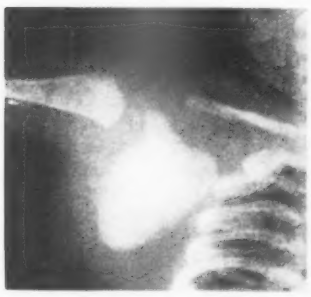

FIG. 1.—27.4.59.

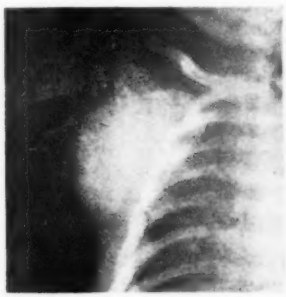

FIG. 2.—6.5.59.

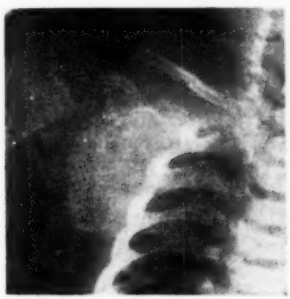

FIG. 3.—1.6.59.

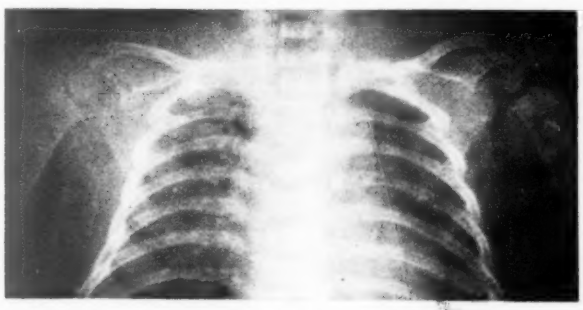

FIG. 4.—29.9.59.

FIGS. 1–4.—The serial radiographic changes in Case I, showing increasing size and density of the scapula and spontaneous return to nearly normal.

stridor and dyspnœa following an insect bite on the previous day.

Examination revealed no abnormality except for breathing difficulty and peri-orbital œdema. A diagnosis of allergic laryngeal œdema was made and treatment with Phenergan produced dramatic improvement. On 23.9.59 it was first noted that she would not move her left arm. The left scapula was found to be enlarged, bony hard but without signs of local inflammation. Radiographs of both the scapula and mandible showed typical changes of infantile cortical hyperostosis.

Investigations.—Temperature 99·4° F, Hb 8·3 g%, W.B.C. 10,200, W.R. and Kahn negative.

Progress.—Limb movements returned spontaneously after three days and have remained normal except for brief periods since. The pyrexia subsided after one week but recurred for a short time in the third week. The mother observed transient facial swelling. The scapula has remained stationary in size but radiographs show improved density and structure of the affected bones.

Discussion.—Infantile cortical hyperostosis begins in the first six months of life with the appearance of soft tissue swelling overlying one or more bones. The bones most frequently affected are the mandible, clavicle and ulna, but lesions in all bones except the vertebræ, pelvis and phalanges have been described. These swellings are neither hot nor red. Frequently there is malaise, difficulty in feeding, fever, mild leucocytosis, slightly raised E.S.R. and raised serum alkaline phosphatase. The Wassermann and Kahn reactions are negative. When the soft tissue swellings are present the radiographs are normal, but most cases are first seen when this stage is presumably passed.

Biopsy at this early stage in a few cases has shown low-grade inflammation of muscle and periosteum (Dickson *et al.*, 1947).

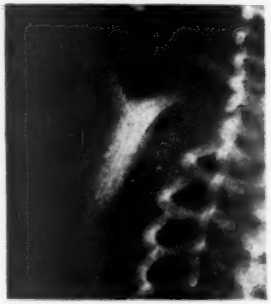

FIG. 5.—Axial view of scapula in early radiological stage of infantile cortical hyperostosis showing subperiosteal new bone (Dr. Carstairs' case).

The tender soft-tissue swellings subside and their place is taken by non-tender bony swellings. Radiographs show an increase in size of the bone due to deposition of subperiosteal new bone (Fig. 5). Decalcification soon takes place and the subperiosteal new bone merges with the rest of the bone. The radiographic appearance is then that of an enlarged bone of subnormal density with a thin shell of dense cortex like that seen in fibrous dysplasia (Figs. 3 and 6). Later

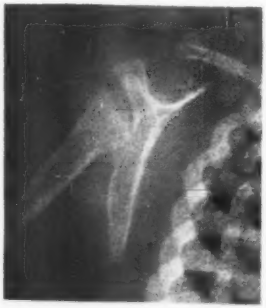

FIG. 6.—Axial view of scapula in Case I in late stage to show merging of new subperiosteal bone with the body of the scapula. Compare with Fig. 1.

the bone resumes its normal size and density. The duration of the disease is usually about six months but may be two to three years. Several causes have been suggested. One is that it is an infective lesion, possibly viral, affecting the muscle and periosteum. Consequent endarteritis causes secondary changes in the bone. The advocates of the infective theory point to the leucocytosis and the raised E.S.R. Those against it point out that there is no local heat, redness, suppuration, lymphadenopathy or change in the antibody titres. Another theory suggests an allergic reaction producing angioneurotic œdema in the subperiosteal tissue followed by reactive deposition of new bone. This hypothesis was put forward by Caffey and Silverman (1945) but not substantiated. The history of Case II is of interest because it suggests a relationship between infantile cortical hyperostosis and allergy due to an insect bite.

Acknowledgments.—Our thanks are due to Dr. Doyne Bell and Mr. David Trevor for permission to publish Case I, to Dr. Ursula James and Mr. R. H. Young for permission to publish Case II, and to Dr. L. S. Carstairs for permission to publish Fig. 5.

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Cortisone Arthropathy of Hip.—RODNEY SWEETNAM, M.B., F.R.C.S.

L. M., a motor mechanic aged 64, attended the London Hospital in March 1955 suffering from rheumatoid arthritis of recent onset.

Having failed to respond to physiotherapy and analgesics, treatment with oral cortisone, 62·5 mg daily, was commenced in August 1955. His general condition and painful joint stiffness improved rapidly, and attempts to discontinue this drug were eventually abandoned owing to considerable increase in pain. He then continued to receive cortisone in this dose until the present day (total of about 90 g).

In February 1958 he complained, for the first time, of pain in his left hip. One injection of hydrocortisone acetate, 125 mg, was given into the joint at that time and his pain was relieved for several weeks.

He has continued to complain of discomfort in this hip, which, although gradually increasing, has never been severe. Only during the past four months has his walking been impeded by pain and this has now been considerably relieved by wearing a weight-relieving caliper.

Examination shows an intelligent man with generalized rheumatoid arthritis. He is entirely independent and walks with a caliper and elbow crutches.

There is 1½ in. (3·8 cm) true shortening of the left leg. Movements of the left hip are accompanied by coarse crepitus but cause surprisingly little discomfort. Pain, however, is experienced at the limits of his range of movement.

Movements of left hip: Flexion 110 degrees, abduction 50 degrees, adduction 40 degrees, external rotation 40 degrees, internal rotation 30 degrees.

Radiological examination shows a diffuse osteoporosis of the whole skeleton but no definite evidence of Cushing's syndrome. The remarkable destructive changes in the left hip joint are shown in Figs. 1 to 3.

Investigations.—W.R. negative. E.S.R. 29 mm in 1 h (Westergren). Hb 86%. Latex test (rheumatoid arthritis) positive 1 : 5120. Anti-staphylococcal alpha-hæmolysin titre normal. Alkaline phosphatase 11 K.-A. units. Serum calcium 9·1, phosphorus 2·9 mg%. Plasma proteins—normal levels.

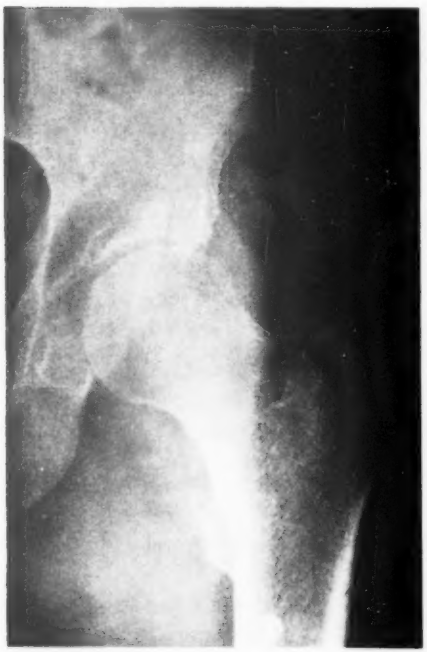

FIG. 1.—April 1957 (after one year eight months of cortisone treatment).

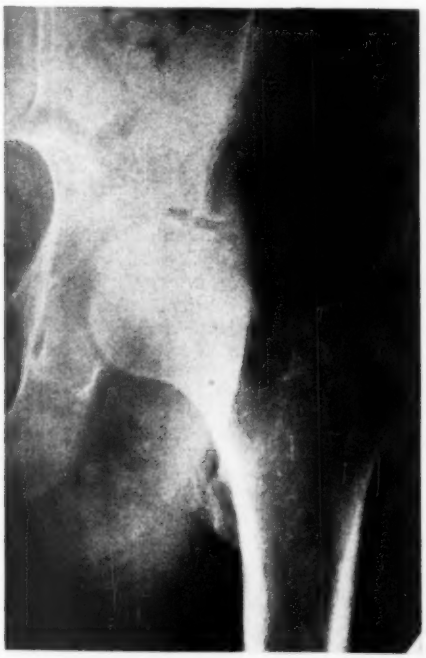

FIG. 2.—February 1958 (after two years five months of cortisone treatment).

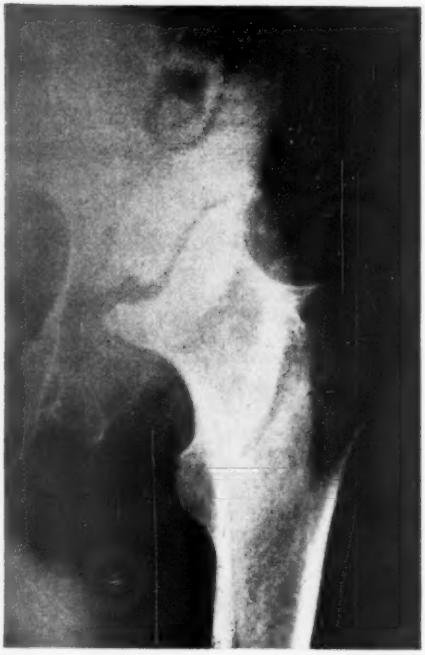

FIG. 3.—May 1959 (after three years nine months of cortisone treatment).

Comment.—The lesion in this hip is thought to be due to prolonged administration of cortisone in high dosage—"cortisone arthropathy". Such rapid destruction of the joint, particularly with so little pain, is seldom, if ever, seen in uncomplicated rheumatoid arthritis.

The relative freedom from pain in the presence of severe joint destruction is similar to Charcot's arthropathy in which diminished pain sense is probably responsible for the startling joint changes.

The analgesic effect of cortisone is well known and, in this patient, most striking. Attempts have been made to reduce his dose but each time he complained so bitterly that the original high dosage was resumed.

Pietrograndi and Mastromarino (1957) first drew attention to the destruction of joints which might occur after prolonged administration of cortisone. They described one case, in which changes, similar to those of this patient, were encountered in the hip after four years of oral cortisone administration for severe pemphigus.

Chandler and Wright (1958), have pointed out the damaging effect of intra-articular injections of hydrocortisone in rheumatoid arthritis and recently Chandler *et al.* (1959) have described a patient with destruction of the femoral head following 18 injections of 50 mg of hydrocortisone into an osteoarthritic hip.

In a review of the effects of cortisone on the skeleton, Murray (1959) has described two further patients whose hips have suffered similar destruction as a result of cortisone administration.

The significance of the damaging effects of cortisone, whether it be given by mouth or by intra-articular injection, is self-evident and the possibility of "Charcot-like" joint changes should always be borne in mind when long-term, or high-dose, therapy is prescribed.

Acknowledgments.—I should like to express my thanks to Dr. W. S. Tegner and to Mr. O. Vaughan-Jackson for permission to record this case.

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MURRAY, R. O. (1959) M.D. thesis, University of Cambridge.
PIETROGRANDI, V., and MASTROMARINO, R. (1957), *Ortop. Traumat. Appar. mot.*, **25**, 791.

The following cases were also shown:

Charcot Shoulders and Charcot Spine.—Mr. W. M. WEARNE (for Mr. DAVID TREVOR).

Subcutaneous Plaque Calcification in Old Thrombosed Veins.—Mr. K. H. STONE (for Mr. DAVID TREVOR).

Coxa Vara.—Dr. F. E. BONNER (for Mr. D. M. DUNN).

Javelin Thrower's Elbow.—Dr. J. E. MILLER (for Mr. H. OSMOND-CLARKE).

(1) Osteoid Osteoma of the Talus. (2) Osteoid Osteoma of the Tibia. (3) Congenital Bipartite Lunate. (4) Congenital Absence of the Lunate.—Dr. A. C. HUME (for Mr. H. OSMOND-CLARKE).

Spontaneous Dislocation of the Lunate in a Boy of 6.—Mr. A. J. HARROLD (for Mr. G. LLOYD-ROBERTS).

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BOOK REVIEWS

Diseases of the Nose, Throat and Ear. By I. Simson Hall, M.B., Ch.B., F.R.C.P.E., F.R.C.S.E. 7th ed. (Pp. xii+467; illustrated, with 8 colour plates. 21s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This textbook remains as popular as ever and the seventh edition is now published only three years after its predecessor. It is revised throughout in detail though there is no major alteration in its layout. Many minor alterations in the text have improved the book and corrected points of criticism.

This book is an excellent introduction to the specialty and is of great value to the newly appointed house surgeon. The index is good and there can be no objection to the absence of references in a textbook of this size and nature.

Mr. Simson Hall is to be congratulated on maintaining the high standard set by the earlier editions and this edition can be highly recommended as a reliable guide to diagnosis and treatment.

An Introduction to Surgery for Dental Students. By R. P. Jepson, F.R.C.S., and B. N. Catchpole, F.R.C.S. (Pp. x+166; illustrated. 21s.) London: English Universities Press. 1959.

The object of this book is to introduce the principles of general surgery to dental students. In this it succeeds for it is concise and clearly explained, it is well produced and the illustrations well chosen. But does it go quite far enough? The student chooses a book which will aid his lectures and clinical work, to which he can refer to supplement and clarify his knowledge and which will be adequate for revision for examination purposes. Few can afford more than one textbook for each subject and the present volume does seem to sacrifice comprehensiveness for brevity. Faced with examination questions on ulcers of the tongue, osteomyelitis and jaw fractures, the student would have some difficulty in supplying satisfactory answers from the text. But brevity is a good fault and what is necessarily sacrificed in the text can often be replaced by suitable diagrams. The reviewer believes that by using such diagrams the one real defect of this book can be overcome, and that such improvement will be found possible in future editions without increase in the present price, which is very reasonable.

Proceedings of the World Congress of Gastroenterology and the Fifty-ninth Annual Meeting of the American Gastroenterological Association, May 25–31, 1958. In 2 volumes. (Pp. xxxv+1363; illustrated. 160s.) London: Baillière, Tindall & Cox. 1959.

These two volumes, containing much new material, include nearly all the papers delivered at the International Congress, and this prompt production is a model of how proceedings of a large congress should be published. Nearly all the 224 papers are in English and panel discussions are included. The congress covered various fields. There were sections and symposia on the following subjects: epidemiology, ætiology and clinical manifestations of peptic ulcer; gastro-intestinal physiology; intestinal infections and infestations; diseases of the liver, biliary tract and pancreas; intestinal malabsorption; higher education of the gastro-enterologist; ulcerative colitis; gastric carcinoma; gastric surgery and its consequences.

The two sections on the epidemiology of peptic ulcer included papers from many different countries, reflecting the increasing interest in the reasons for the patchy incidence of peptic ulcer throughout the world. It is difficult to pick out individual papers from such a mass of material. Ivy produced good evidence that histamine is a gastric secretory hormone. A team containing Stewart Wolf described methods for more accurate fractionation of gastric juice components. Dreiling and Janowitz introduced a new theory about the method of bicarbonate production by the pancreas. Mollin and his colleagues gave a paper on the pathogenesis of vitamin B_{12} and folic acid deficiencies in steatorrhœa. Bean discussed rare causes of upper intestinal bleeding. Shiner and Doniach's extensive work on jejunal biopsy is here published at some length.

This collection of papers would be a useful addition to any gastroenterologist's library.

Surgical Treatment of Bone and Joint Tuberculosis. By Robert Roaf, M.A., M.Ch.Orth., F.R.C.S.Ed., F.R.C.S.Eng., W. H. Kirkaldy-Willis, M.A., M.D., B.Chir., F.R.C.S.Ed., and A. J. M. Cathro, M.B., Ch.B. (Pp. viii +137; 90 illustrations. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This is essentially a practical handbook, written to help those general surgeons working in countries less developed than our own where surgical tuberculosis is still a major problem. In the past the lack of facilities, different social cus-

toms and the severity of the cases when first seen must have made conservative treatment, as it is usually understood, heartbreakingly disappointing. With the advent of streptomycin and effective chemotherapeutic agents the whole picture of what can be offered to these people has changed. Direct surgical attack on the focus is now possible without the old danger of sinus formation and disastrous secondary infection. Treatment is shortened and no longer is bony ankylosis necessarily the most favourable outcome.

This book gives succinct guidance on what to do in each case, when to do it, and how to do it, the authors drawing from their wide experience to restrict their recommendations always to what is practicable in the conditions they envisage. Your reviewer has nothing but praise for this book, which will be read with interest and profit by all who have contact with bone and joint tubercle, an admittedly diminishing band in this country.

Synopsis of Ear, Nose, and Throat Diseases. By Robert E. Ryan, B.S., M.D., M.S.(ALR), F.A.C.S., William C. Thornell, A.B., B.M., M.D., M.S.(ALR), F.A.C.S., and Hans von Leden, M.D., F.A.C.S., F.I.C.S. (Pp. 383; illustrated. 50s.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1959.

This book is truly a synopsis and not a textbook. It would be totally inadequate as a textbook, but as a synopsis it is excellent. It is very well printed and the illustrations are good.

Each section begins with chapters on the anatomy and the physiology of the organ. These are brief, clear and easily understood.

Each disease is described and then followed by a very brief summary of the symptoms and treatment. Under treatment, definite advice is given and the reader is left in no doubt about what the authors recommend. In this respect this book is better than, and unlike, many textbooks which enumerate many possible treatments but leave the reader uninformed about what treatment the author advises. This feature will be much appreciated by housemen, and doctors who are not specialists.

The reviewer particularly liked the chapter entitled tracheotomy which gives a brief but comprehensive list of indications and definite sensible advice about the indications for the operation and for intubation.

The index is adequate and the book is small and compact so that it will fit into a large pocket.

This synopsis can be strongly recommended as a useful aid for practitioners unfamiliar with ear, nose and throat work, and as a reliable guide to the management of the common and simple disorders of the specialty.

Transplantation of Tissues. Vol. 2. Edited by L. A. Peer, M.D. (Pp. xiii+690; 252 illustrations. 160s.) London: Baillière, Tindall & Cox. 1959.

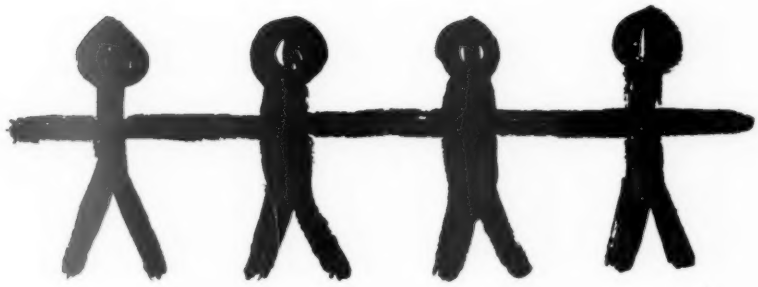
Volume 1 of "Transplantation of Tissues" was the effort of Lyndon Peer alone. Volume 2 is a joint effort by thirteen contributors who are well known for their work in this field of medicine and biology. The following tissues in the transplanted state have been discussed at length; skin, cornea, fat, nerves, teeth, blood vessels, endocrine glands, kidney, heart, lung, liver and spleen, peritoneum and tumours. In addition, there is a chapter on tissue culture, another by P. B. Medawar on the zoologic laws of transplantation, and a very impressive chapter by Lyndon Peer himself on the structure and behaviour of cells. Animal and human experiments have been meticulously recorded wherever possible. The book is very readable and up to date with its information. The data from varied sources imply that the destruction which is the fate of most homotransplants is mediated by an immunological process. There would seem to be a lack of critical assessment of this aspect. However, this volume will remain the standard reference book on tissue transplantation for many years to come. The authors are to be congratulated for their meticulous work. Experimentalists will be for ever grateful to Lyndon Peer and his co-authors for rendering them such a magnificent and timely service. No transplanter should be without it!

The Medical Annual, 1959. Edited by R. Bodley Scott, M.A., D.M., F.R.C.P., and R. Milnes Walker, M.S.(Lond.), F.R.C.S. (Pp. xl+620+19; illustrated. 42s.) Bristol: John Wright & Sons, Ltd. 1959.

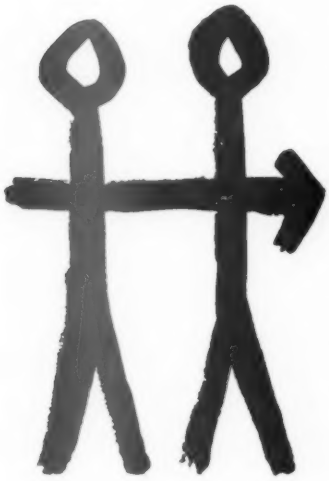
Every year when the Medical Annual is published we cannot but feel grateful to the editors and contributors alike, as their efforts illuminate not only the paths we rarely travel, but also those we habitually follow, and by their efforts they reduce some of our burden in keeping up with the literature.

Our special gratitude is due to Sir Henry Tidy whose photograph graces this edition. He has for many years served the Annual and has now retired from the editorship, leaving behind a very high standard that is being fully maintained by his successor, Dr. R. Bodley Scott.

The subjects and authors of the special articles —fluid and electrolyte balance, emphysema, cancer research, new sex hormones, cross-infection in wards—are skilfully chosen, and these are followed by invaluable reviews of the year's work. These reviews involve a great deal of careful



10 unknown diabetics in every GP's care...



The diabetic population of Great Britain numbers almost 500,000—yet only about half of them are known and under treatment. Statistically this means that every general practitioner has more than ten undetected diabetics in his care.
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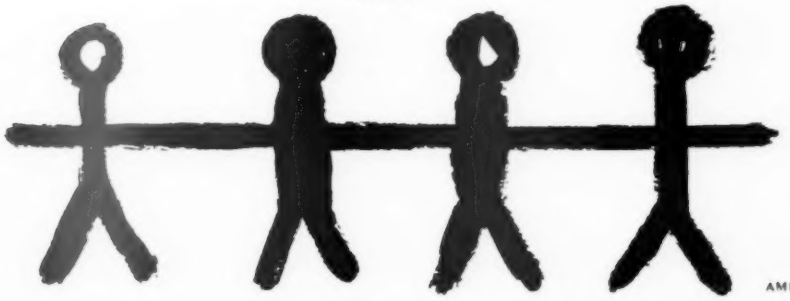

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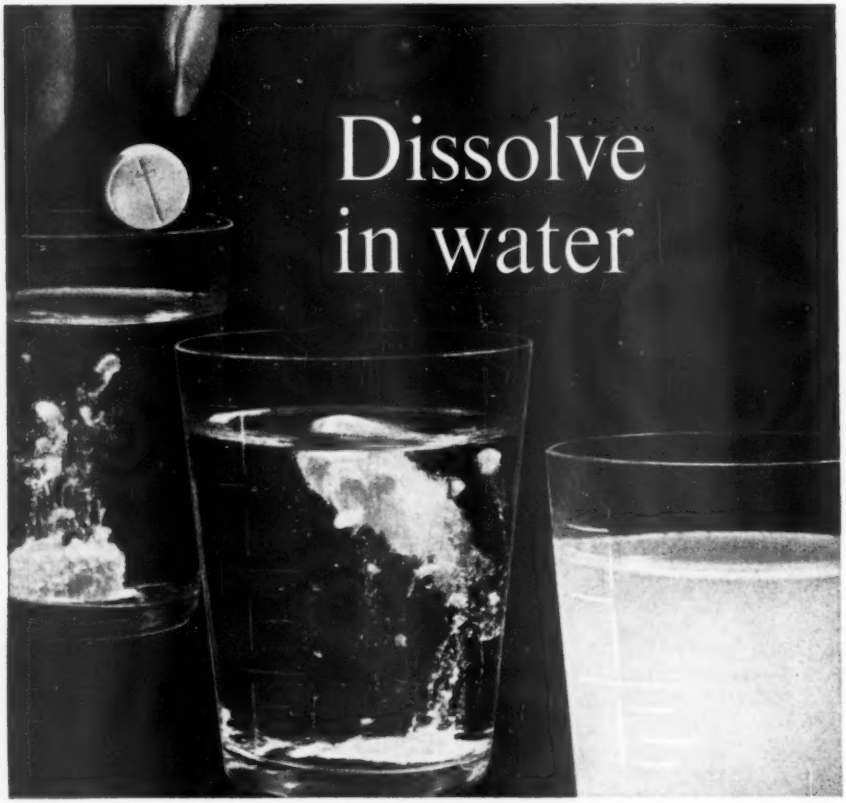

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selection, and it is notable that the individual contributors succeed in avoiding, wherever they can, overlapping with the preceding year, although rapidly changing subjects are kept constantly before the reader.

Two guineas is not a high price for so much.

Midwifery. (A textbook for pupil midwives.) By Gordon W. Garland, M.D., F.R.C.O.G., and Rosemary C. Perkes, S.R.N., S.C.M., M.T.D. (Pp. xi+290; illustrated. 21s.) London: The English Universities Press Ltd. 1959.

This textbook for pupil midwives has been written by Mr. Garland, obstetrician to St. Thomas's and the General Lying-in Hospital and by Miss Perkes, the Matron of the General Lying-in Hospital. It is intended to cover the syllabus for Part I of the Examinations of the Central Midwives Board.

Mr. Garland is experienced in writing textbooks for the nursing profession, and his "Obstetrics and Gynæcology for Nurses" is already well known. This book maintains a high standard of clarity of expression. The glossary which forms Chapter II will prove invaluable to those new to the subject. In short this book admirably performs its function of providing a new and up-to-date textbook for pupil midwives. It is compact yet readable, well printed and well produced and the illustrations are adequate.

Clinical Effects of Electrolyte Disturbances. The Proceedings of a Conference held in London at the Royal College of Physicians of London, February 27–28, 1959. Edited by E. J. Ross. (Pp. x+210; illustrated. 20s.) London: Pitman Medical Publishing Co. Ltd. 1959.

To address its Conference on the Clinical Effects of Electrolyte Disturbances the Royal College of Physicians assembled a team of 21 experts, and in this excellent volume their papers are reproduced in full, together with the ensuing discussions. The opening session considered the methods of studying disturbances of body fluid balance; thereafter the sessions were devoted to œdema and its control, kidneys and electrolytes, endocrines and electrolytes and, finally, general aspects. Each of these sections is packed with information, and throughout the practical, clinical aspects of the various subjects are admirably blended with basic, physiological considerations.

From the many contributions of a uniformly high standard it is, perhaps, invidious to select individual papers for mention, and it must suffice to say that the principles of balance studies, potassium depletion, renal failure, and electrolyte disturbance in diabetes mellitus are among the subjects which are admirably discussed. Surgical interests are catered for by the sections on the metabolic response to trauma and electrolyte disturbances in diseases of the gastro-intestinal tract.

Sensibly produced, at a modest price, and containing very adequate references, this book is a credit to all concerned in its production. Although ". . . aimed particularly at the consultant, not at the man in training . . ." it should be of the greatest value to physicians whatever their status and whether or not they have a special interest in this important field of work. Surgeons, also, will find much of value in many of the papers. Containing in a small compass a wealth of information lucidly set out, this book is a valuable addition to British medical literature.

The Cervical Syndrome. By Ruth Jackson, B.A., M.D., F.A.C.S. 2nd ed. (Pp. viii+197; illustrated. 50s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications, Ltd. 1958.

A second edition of this monograph has appeared after two years. Its enlargement by the addition of over 60 pages and 40 illustrations is not surprising, since the author's conception of what constitutes the cervical syndrome is liberal in the extreme. The syndrome is defined as embracing the clinical features that occur "as a result of irritation or compression of cervical nerve roots in and about the intervertebral foramina"; but it includes periarthritis of the shoulder, strain of the extensor origin from the lateral humeral epicondyle, and even cervical sympathetic nervous irritation with such resulting symptoms as ocular pain, blurred vision and vertigo.

In the ætiology of the syndrome, such recognizable lesions as vertebral subluxations and fractures and osteophyte formations in the intervertebral foramina are discussed, as also is a series of purely hypothetical lesions—œdematous capsular ligaments, dural nerve sheaths, nerve roots themselves, toxic capsulitis and emotional stress. It is even suggested that posterior displacement of the vertebral artery may give rise to the syndrome. The author is apparently convinced that a cervical intervertebral disc protrusion cannot be responsible for cervical and brachial pain in the absence of evidence of a cord lesion—a view which indicates not only a readiness to discard the evidence produced by competent surgeons, but a lack of experience of the living pathology of the cervical spine.

The author's approach to her subject is perhaps

of most value in indicating that, since many of the less serious causes of cervical and brachial pain (including, though it is not so stated, intervertebral disc protrusions) heal spontaneously, a conservative approach to therapy is indicated.

Modern Trends in Pathology. Edited by Douglas H. Collins, O.B.E., M.D.(L'pool), F.R.C.P. (Lond.) (Pp. x+334+12; illustrated. 70s.) London: Butterworth & Co. (Publishers) Ltd. 1959.

This volume is concerned with some of the "growing points" of pathology, and many different topics are considered, ranging from the light thrown by new methods on the biochemical basis of cellular pathology to the problems raised by examination of pathological tissue in the fresh state, and injury to connective tissue. The localization of antibody production, endogenous mechanisms in the acute inflammatory reaction and whole body irradiation are also discussed.

Three chapters are concerned with tumours of various kinds—some uncommon and recently identified neoplasms, cancer in Africa and cancer of the liver. Also discussed are disorders arising from the human trophoblast, movements of neurotoxins and neuroviruses in the nervous system, 5-hydroxytryptamine, the adrenal cortex in disease, occupational pulmonary diseases and pathological ossification and osseous metaplasia in man.

Each chapter is authoritative and each has a pleasant individuality of style. The editor is to be congratulated on the choice of subjects and contributors. The book is admirably produced. There is a useful and comprehensive list of references, and the illustrations are first class. The whole production will be of value to those who wish to be familiar with modern trends in pathology.

The Thyroid Hormones. By Rosalind Pitt-Rivers, M.Sc., Ph.D.London, F.R.S., and Jamshed R. Tata, M.Sc.Bangalore, Docteur ès Sciences, Paris. (Pp. xiii+247; 22 illustrations. 50s.) London, &c.: Pergamon Press. 1959.

This book is the first of a new series of international monographs to be published by the Pergamon Press. It is an admirable survey of the thyroid hormones and is clearly written in excellent English. The chemistry of these hormones, the methods by which they are manufactured in the thyroid gland and transported in the blood stream, and their resulting physiological action on target organs are clearly described. The hypotheses which have been so far put forward to explain the action of the thyroid hormones are well outlined and the metabolism of iodine in the body has a section all to itself.

Dr. W. R. Trotter has contributed a chapter on diseases of the thyroid which is a neat, if brief, exposition. It is very useful when read in conjunction with the rest of the book. There are some 1,774 references which make this a most valuable monograph for the library. There is no other publication comparable with this one at the present time and it is an extremely welcome addition to the bibliography of the thyroid.

More Medical and Other Verses. By Alex E. Roche. (Pp. viii+35. 5s.) London: H. K. Lewis & Co. Ltd. 1959.

That surgeons don't write verse is no reproach; their talents are revealed in other ways. All the more credit then to Mr. Roche who has just published this small book of lays. Though inspiration here and there may nod, some melody and beauty will be found, and while his rhymes are sometimes rather odd the whole effect gives quite a pleasing sound.

The subjects of the verses may seem strange; they go from "Life" to "Liver", "Bart's" to "Hearts", "Venice", "A Motor Car", "A Mountain Range", and quite a lot about man's inward parts. So I would offer them a modest praise for one may catch the true authentic ring, and, anyway, in these disturbing days it does one good to hear a surgeon sing.

International Review of Neurobiology. Edited by Carl C. Pfeiffer and John R. Smythies. Vol. I. (Pp. xii+383; illustrated. $10.) New York: Academic Press, Inc. 1959.

This interesting volume appears to be the first of an annual series. The variety of scientific disciplines exemplified indicates that at last the study of the nervous system is transcending in its approach the purely electrophysiological and that the chemical morphology of the nerve cell, and its biochemistry, is coming under intensive study.

This suggests also that problems that must immediately concern the neuropathologist, in so far as he is an experimental pathologist, and not merely a microscopist, should now begin to receive some of the illumination that has been wanting for so long, and that we may gain more knowledge of the ætiology and pathogenesis of nervous diseases than the old classical neurophysiology has afforded.

For all but the specialist some of the chapters will prove hard reading, but the reviewer must

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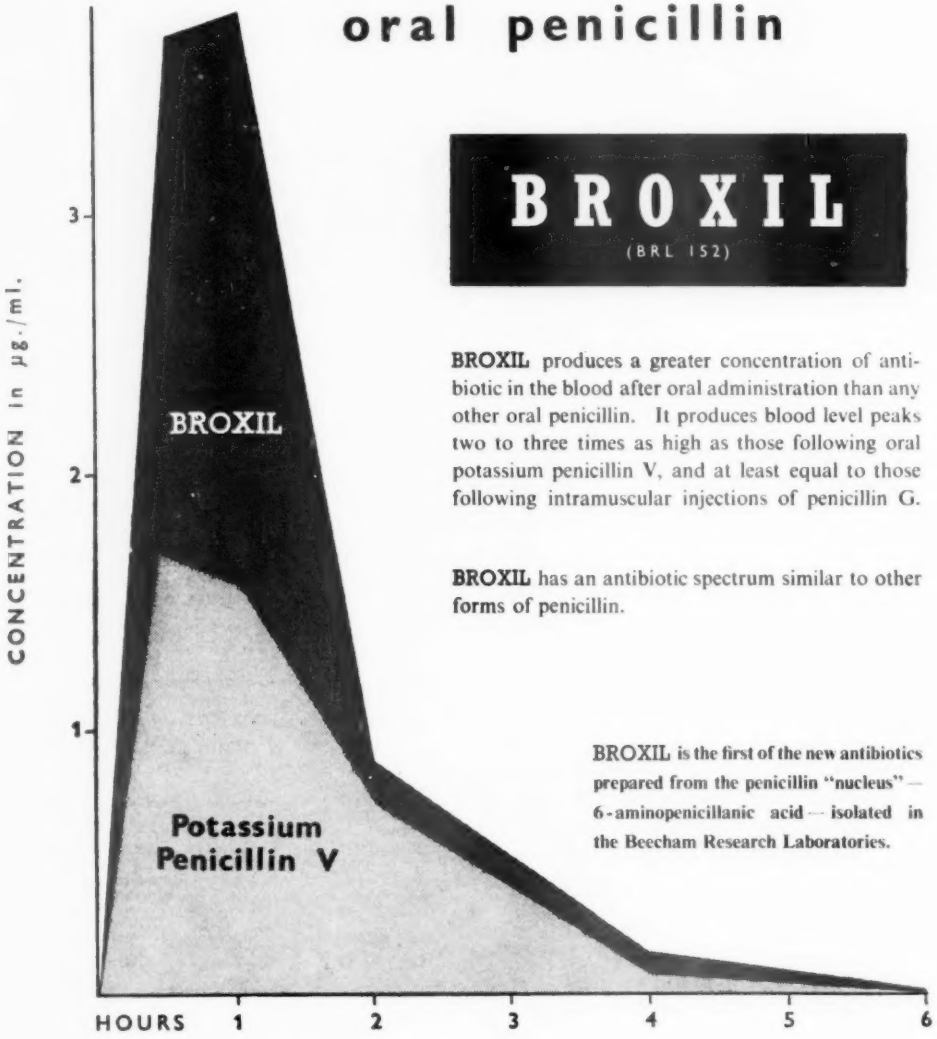

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single out an admirable chapter by Dr. Catherine Hebb on the chemical agents in the nervous system. This presents critically and clearly what has been learned of the chemical morphology of the cell, of the plan of its enzyme systems, and of the problems arising from the study of chemical transmitters, of chemical excitatory and inhibitory substances. This chapter is a must for the clinical neurologist.

Equally valuable is Dr. Purpura's critical review of the nature of electrocortical potentials and synaptic organizations in the cerebral and the cerebellar cortex.

Not all the articles are as cautious and as clear and concise as these two, but all are of a high level, and the volume is a valuable one for the neurologist who wishes to keep abreast with the several sciences basic to his discipline.

Tools of Biological Research. Edited by Hedley J. B. Atkins, D.M., M.Ch.Oxf., F.R.C.S. Eng., Hon. F.A.C.S. (Pp. xvi+183; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

This book consists of ten lectures on fundamental techniques in experimental work and covers a very wide field from such subjects as flame photometry and tissue culture to electrophoresis and image intensification. These lectures were given at a Conference held at Guy's Hospital in 1958 and the way in which the Conference was convened is particularly interesting. Hedley Atkins explains in his preface that it was really due to the Surgical Research Society. This Society was formed in 1956 largely as a result of the enterprise of David Patey, Director of the Department of Surgical Studies at the Middlesex Hospital. At its meetings, some of the senior members found that they were unfamiliar with many of the tools being used in the various research projects under discussion. For this reason Hedley Atkins decided to hold a two-day symposium on techniques and entitled it "Tools of Biological Research". He also had the inspiration to invite Sir Cyril Hinshelwood, the President of the Royal Society, to give the introductory address.

It is these admirable lectures, carefully edited and printed, which comprise the book under review. Each chapter has a good list of references, which are extremely useful as the titles of the papers are given in full. There are many illustrations, some of them in colour, and the whole publication is beautifully produced. This is an admirable book for any library or research department and a very good introduction for the research worker who is looking to a new technique to help him in some particular problem.

The Care of Minor Hand Injuries. By Adrian E. Flatt, M.A., M.D., F.R.C.S. (Pp. 266; 109 illustrations. 71s. 6d.) St. Louis: The C. V. Mosby Company. 1959.

This book should be part of the equipment of every Casualty Department. In an organ of such vital importance to us as the hand, even the so-called minor injuries may have complications so menacing that even the most trivial must be treated with knowledge, care and circumspection. This book tells you how to do it. It is eminently practical, based on very wide personal experience, pleasantly interspersed with touches of humour, and notable for a refreshing honesty about the difficulties of such procedures as extensor tendon repairs, so often glossed over as simple outpatient affairs within the capabilities of all and sundry. The more complicated the subject the more important to the student is the style and "readability" of the author; on this count Dr. Flatt takes full marks. Anyone whose duties include the care of the injured hand will read this little book with pleasure and profit.

Aldosterone in Clinical and Experimental Medicine. By E. J. Ross, M.D., Ph.D., M.R.C.P. (Pp. viii+144. 22s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Steroid chemists, biologists, research workers and clinicians interested in aldosterone will all be grateful to Dr. Ross for succinctly marshalling in 114 pages all that is currently known about this hormone. The facts, based on 539 references, are clearly stated in excellent English, and speculation is at a minimum. Such a book is of great value in giving a balanced account of the present position of aldosterone. The author must be congratulated on his industry and accurate assembling of the data.

Cancer in Families. A Study of the Relatives of 200 Breast Cancer Probands. By Douglas P. Murphy, M.D., and Helen Abbey, Sc.D. (Pp. x + 76. 20s.) Cambridge, Mass.: Harvard University Press (Commonwealth Fund). London: Oxford University Press. 1959.

What on earth, most doctors would ask, is a proband? And they would have to read this word thirty-six times and reach page 10 before finding a definition of it. Statisticians have only themselves to blame if their writings are sometimes regarded with impatience: they should think of lesser mortals and take their heads out of the clouds. The word proband has of course a precise meaning, namely an individual in whose family the occurrence of a characteristic is to be studied.

This is an important little book though unfortunately it is not at all readable. An immense amount of painstaking work has gone into the investigation of nearly 12,000 individuals, the relatives of 200 cancer probands and 198 control probands. It was originally planned to determine whether cancer of the breast occurs more often among the female relatives of a woman who has had this disease; but as the study proceeded male relatives and cancer at all sites were included. The details cannot well be summarized but the conclusion is clear: no evidence is shown for any liability to cancer either of the breast or elsewhere, among the relatives of a woman who has cancer of the breast.

Treatment of Cancer in Clinical Practice. Edited by P. B. Kunkler, M.A., M.D. (Cantab.), M.R.C.P., F.F.R., and Anthony J. H. Rains, M.S.(Lond.), F.R.C.S. (Pp. xvi+821; illustrated. £5) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

Recent years have seen the appearance of a number of comprehensive, multiple-volume treatises on cancer which from their bulk can serve only for reference. The present volume has different aims. A radiotherapist and a surgeon have combined to write and edit a book limited to the treatment of cancer. The readers that they have particularly in mind are candidates preparing for postgraduate diplomas in surgery and radiology, and they hope that each discipline will benefit by knowing something of the principles and techniques used by the other. In the first 150 pages they enunciate general principles and in the remaining 650 they discuss the applications of these principles to cancer in particular regions, calling where necessary on appropriate experts. In most of these latter chapters a surgeon and a radiologist have combined in the writing, and give valuable reasoned statements on the relative positions of surgery and radiation in the treatment of cancer in individual sites. This constitutes an interesting and educative approach. The only major criticisms of the present work are, firstly, a doubt whether it is necessary for the embryo surgeon to know quite so much about the technique as opposed to the principles and results of radiological treatment, and, secondly, a query whether some of the introductory chapters are not too diffuse. With modification on these two points, the authors might in a second edition produce a shorter and consequently even more valuable book. As a small final point, it is a pity that the authors have not followed the increasingly prevalent convention of giving titles with references, a convention which makes a reference list so much more valuable.

A Textbook of Surgical Physiology. By R. Ainslie Jamieson, M.B., F.R.C.S.Ed., and Andrew W. Kay, M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S.G. (Pp. vii+623; 186 illustrations. 55s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

In the past twenty years surgical thought has become increasingly concerned with physiological and biochemical problems. British surgical research workers have been to the forefront in developing and exploiting this new field of surgical endeavour, but hitherto there has been no British textbook on this subject. Mr. Jamieson and Professor Kay have set out to fill this gap. In a book designed for the postgraduate student they aim to discuss "those aspects of applied physiology which are fundamental to the practice of general surgery". Beginning with chapters on general topics such as wound healing and the biological effects of irradiation, each system of the body is then dealt with in turn, omitting from consideration only the female reproductive organs and the central nervous system. Each chapter includes a short but select list of references for further reading.

In general the essential physiological facts concerning each organ and system are clearly set out and their clinical significance is succinctly underlined. However, the book is not altogether satisfactory. Surgical physiology covers a wide range of subjects in which significant advances are constantly being made, and it is accordingly difficult for two authors to cover all the topics adequately. This difficulty is reflected in the uneven quality of the various chapters, and in the rather stilted, conventional approach to some subjects. Thus the description of the metabolic response to trauma is in many ways unsatisfactory: in particular, a good deal of recent work on the subject receives no mention, and the period of impaired renal excretion of sodium is misleadingly referred to as a period of sodium retention. The chapter on respiratory problems, whilst containing much valuable information, is not in line with the modern approach to the subject. The description of the maintenance of acid-base balance is couched in terms which make it wellnigh impossible to grasp the problems involved, and it is a great pity that this subject is not discussed in terms of hydrogen-ion concentration. In contrast, the chapter on gastric physiology is a masterly review of the subject, the problems of thyroid function are admirably discussed, and the basic considerations of body fluid balance are clearly set out. This is not a book for the expert, and in parts must be read by anyone with circumspection. But in its declared aim of introducing the postgraduate student to the subject of surgical physiology it will certainly prove of value.

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* Lancet, 1957 *ii*, 1157

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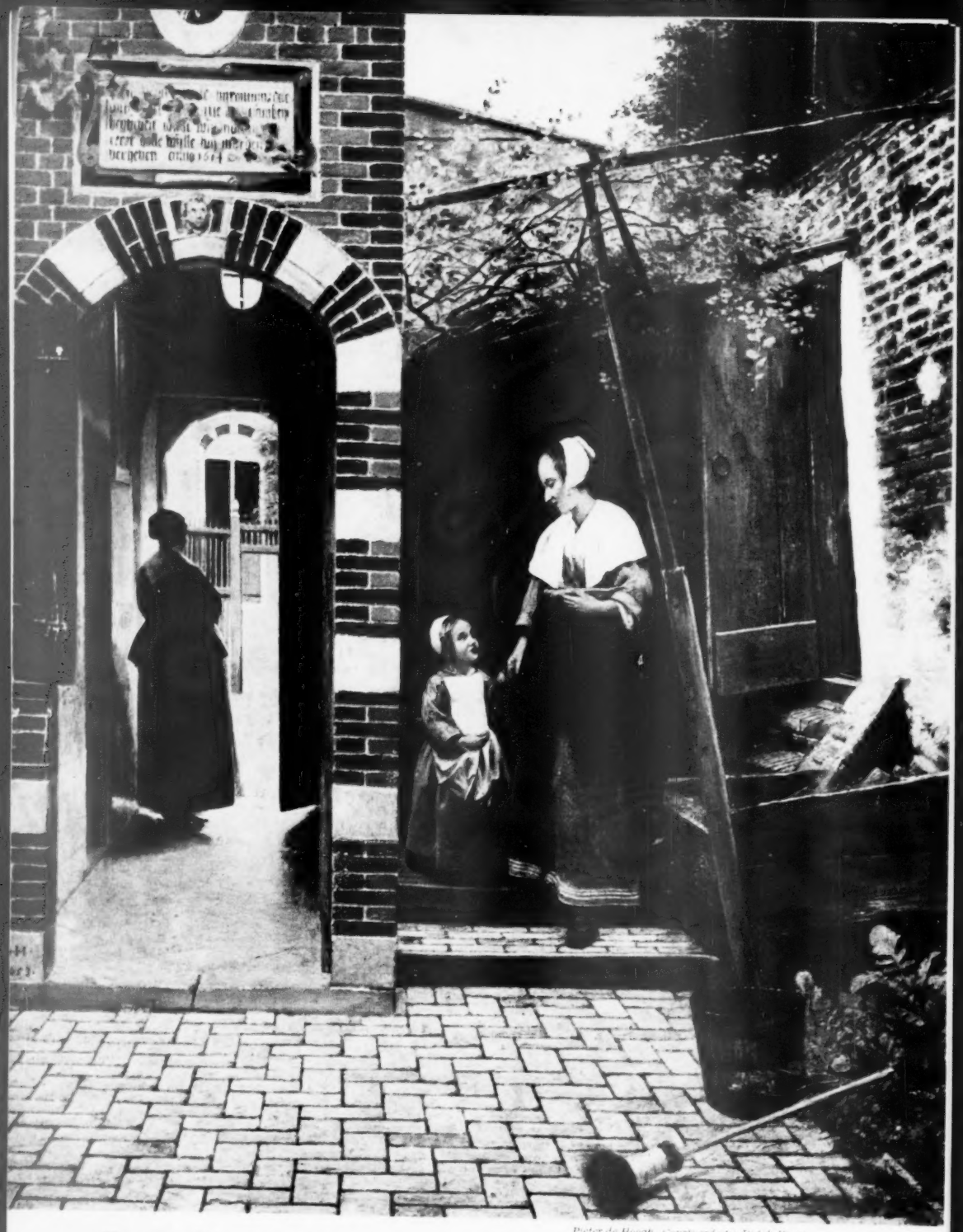

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